CENTER FOR DRUG EVALUATION AND RESEARCH APPROVAL PACKAGE FOR:

APPLICATION NUMBER 21-007/SE7-006 21-039/SE7-006

Final Printed Labeling

2 AGENERASE®

- 3 (amprenavir)
- 4 Capsules

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PATIENT INFORMATION INCLUDED

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Because of the potential risk of toxicity from the large amount of the excipient propylene glycol contained in AGENERASE Oral Solution, that formulation is contraindicated in infants and children below the age of 4 years and certain other patient populations and should be used with caution in others. Consult the complete prescribing information for AGENERASE Oral Solution for full information.

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- DESCRIPTION: AGENERASE (amprenavir) is an inhibitor of the human
- immunodeficiency virus (HIV) protease. The chemical name of amprenavir is (3S)-
- tetrahydro-3-furyl N-[(1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-
- hydroxypropyl]carbamate. Amprenavir is a single stereoisomer with the (3S)(1S,2R)
- configuration. It has a molecular formula of $C_{25}H_{35}N_3O_6S$ and a molecular weight of 505.64.
- 19 It has the following structural formula:

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- 23 Amprenavir is a white to cream-colored solid with a solubility of approximately
- 24 0.04 mg/mL in water at 25°C.

25	AGENERASE Capsules are available for oral administration in strengths of 50 and 150 mg.
26	Each 50-mg capsule contains the inactive ingredients d-alpha tocopheryl polyethylene glycol
27	1000 succinate (TPGS), polyethylene glycol 400 (PEG 400) 246.7 mg, and propylene glycol
28	19 mg. Each 150-mg capsule contains the inactive ingredients TPGS, PEG 400 740 mg, and
29	propylene glycol 57 mg. The capsule shell contains the inactive ingredients d-sorbitol and
30	sorbitans solution, gelatin, glycerin, and titanium dioxide. The soft gelatin capsules are
31	printed with edible red ink. Each 150-mg AGENERASE Capsule contains 109 IU vitamin E
32	in the form of TPGS. The total amount of vitamin E in the recommended daily adult dose of
33	AGENERASE is 1744 IU.
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35	MICROBIOLOGY:
36	Mechanism of Action: Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to
37	the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol
38	polyprotein precursors, resulting in the formation of immature non-infectious viral particles.
39	Antiviral Activity in Vitro: The in vitro antiviral activity of amprenavir was evaluated
40	against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4,
41	CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration
42	(IC50) of amprenavir ranged from 0.012 to 0.08 μM in acutely infected cells and was 0.41 μM
43	in chronically infected cells (1 μ M = 0.50 mcg/mL). Amprenavir exhibited synergistic anti-
44	HIV-1 activity in combination with abacavir, zidovudine, didanosine, or saquinavir, and
45	additive anti-HIV-1 activity in combination with indinavir, nelfinavir, and ritonavir in vitro.
46	These drug combinations have not been adequately studied in humans. The relationship
47	between in vitro anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in
48	humans has not been defined.
49	Resistance: HIV-1 isolates with a decreased susceptibility to amprenavir have been selected
50	in vitro and obtained from patients treated with amprenavir. Genotypic analysis of isolates
51	from amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in
52	amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V
53	as well as mutations in the p7/p1 and p1/p6 gag cleavage sites. Phenotypic analysis of HIV-1
54	isolates from 21 nucleoside reverse transcriptase inhibitor- (NRTI-) experienced, protease
55	inhibitor-naive patients treated with amprenavir in combination with NRTIs for 16 to

48 weeks identified isolates from 15 patients who exhibited a 4- to 17-fold decrease in susceptibility to amprenavir in vitro compared to wild-type virus. Clinical isolates that exhibited a decrease in amprenavir susceptibility harbored one or more amprenavir-associated mutations. The clinical relevance of the genotypic and phenotypic changes associated with amprenavir therapy is under evaluation. Cross-Resistance: Varying degrees of HIV-1 cross-resistance among protease inhibitors have been observed. Five of 15 amprenavir-resistant isolates exhibited 4- to 8-fold decrease in susceptibility to ritonavir. However, amprenavir-resistant isolates were susceptible to either indinavir or saquinavir.

CLINICAL PHARMACOLOGY:

Pharmacokinetics in Adults: The pharmacokinetic properties of amprenavir have been studied in asymptomatic, HIV-infected adult patients after administration of single oral doses of 150 to 1200 mg and multiple oral doses of 300 to 1200 mg twice daily.

Absorption and Bioavailability: Amprenavir was rapidly absorbed after oral administration in HIV-1-infected patients with a time to peak concentration (t_{max}) typically between 1 and 2 hours after a single oral dose. The absolute oral bioavailability of amprenavir in humans has not been established.

Increases in the area under the plasma concentration versus time curve (AUC) after single oral doses between 150 and 1200 mg were slightly greater than dose proportional. Increases in AUC were dose proportional after 3 weeks of dosing with doses from 300 to 1200 mg twice daily. The pharmacokinetic parameters after administration of amprenavir 1200 mg b.i.d. for 3 weeks to HIV-infected subjects are shown in Table 1.

Table 1: Average (%CV) Pharmacokinetic Parameters

After 1200 mg b.i.d. of Amprenavir Capsules (n = 54)

C _{max}	t _{max}	AUC ₀₋₁₂	C_{avg}	C_{min}	CL/F
(mcg/mL)	(hours)	(mcg•h/mL)	(mcg/mL)	(mcg/mL)	(mL/min/kg)
7.66 (54%)	1.0 (42%)	17.7 (47%)	1.48 (47%)	0.32 (77%)	19.5 (46%)

The relative bioavailability of AGENERASE Capsules and Oral Solution was assessed in

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84	healthy adults. AGENERASE Oral Solution was 14% less bioavailable compared to the
85	capsules.
86	Effects of Food on Oral Absorption: The relative bioavailability of AGENERASE
87	Capsules was assessed in the fasting and fed states in healthy volunteers (standardized
88	high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate).
89	Administration of a single 1200-mg dose of amprenavir in the fed state compared to the fasted
90	state was associated with changes in C_{max} (fed: 6.18 ± 2.92 mcg/mL, fasted:
91	9.72 ± 2.75 mcg/mL), t_{max} (fed: 1.51 \pm 0.68, fasted: 1.05 \pm 0.63), and AUC _{0-∞} (fed:
92	22.06 ± 11.6 mcg•h/mL, fasted: 28.05 ± 10.1 mcg•h/mL). AGENERASE may be taken with
93	or without food, but should not be taken with a high-fat meal (see DOSAGE AND
94	ADMINISTRATION).
95	Distribution: The apparent volume of distribution (Vz/F) is approximately 430 L in healthy
96	adult subjects. In vitro binding is approximately 90% to plasma proteins. The high affinity
97	binding protein for amprenavir is alpha ₁ -acid glycoprotein (AAG). The partitioning of
98	amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase,
99	reflecting the higher amount of unbound drug at higher concentrations.
100	Metabolism: Amprenavir is metabolized in the liver by the cytochrome P450 3A4
101	(CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the
102	tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have
103	been identified as minor metabolites in urine and feces.
104	Elimination: Excretion of unchanged amprenavir in urine and feces is minimal.
105	Approximately 14% and 75% of an administered single dose of ¹⁴ C-amprenavir can be
106	accounted for as radiocarbon in urine and feces, respectively. Two metabolites accounted for
107	>90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir
108	ranged from 7.1 to 10.6 hours.
109	Special Populations: Hepatic Insufficiency: AGENERASE has been studied in adult
110	patients with impaired hepatic function using a single 600-mg oral dose. The $AUC_{0-\infty}$ was
111	significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•h/mL) compared
112	with healthy volunteers (12.00 \pm 4.38 mcg \bullet h/mL). The AUC $_{0-\infty}$ and C $_{max}$ were significantly

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113	greater in patients with severe cirrhosis (AUC _{0-∞} : 38.66 ± 16.08 mcg•h/mL; C _{max} :
114	9.43 \pm 2.61 mcg/mL) compared with healthy volunteers (AUC _{0-∞} : 12.00 \pm 4.38 mcg•h/mL:
115	C _{max} : 4.90 ± 1.39 mcg/mL). Patients with impaired hepatic function require dosage
116	adjustment (see DOSAGE AND ADMINISTRATION).
117	Renal Insufficiency: The impact of renal impairment on amprenavir elimination in adult
118	patients has not been studied. The renal elimination of unchanged amprenavir represents <3%
119	of the administered dose.
120	Pediatric Patients: The pharmacokinetics of amprenavir have been studied after either
121	single or repeat doses of AGENERASE Capsules or Oral Solution in 84 pediatric patients.
122	Twenty HIV-1-infected children ranging in age from 4 to 12 years received single doses from
123	5 mg/kg to 20 mg/kg using 25-mg or 150-mg capsules. The C _{max} of amprenavir increased less
124	than proportionally with dose. The $AUC_{0-\infty}$ increased proportionally at doses between 5 and
125	20 mg/kg. Amprenavir is 14% less bioavailable from the liquid formulation than from the
126	capsules; therefore AGENERASE Capsules and AGENERASE Oral Solution are not
127	interchangeable on a milligram-per-milligram basis.
128	AGENERASE Oral Solution is contraindicated in infants and children below the age of
129	4 years due to the potential risk of toxicity from the large amount of the excipient propylene
130	glycol. Please see the complete prescribing information for AGENERASE Oral Solution fo
131	full information.
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Table 2: Average (%CV) Pharmacokinetic Parameters in Children Ages 4 to 12 Years

Receiving 20 mg/kg b.i.d. or 15 mg/kg t.i.d. of AGENERASE Oral Solution

		C _{max}	t _{max}	AUC _{ss} *	C_{avg}	C_{min}	CL/F
Dose	n	(mcg/mL)	(hours)	(mcg•h/mL)	(mcg/mL)	(mcg/mL)	(mL/min/kg)
20 mg/kg		6.77	1.1	15.46	1.29	0.24	29
b.i.d.	20	(51%)	(21%)	(59%)	(59%)	(98%)	(58%)
15 mg/kg		3.99	1.4	8.73	1.09	0.27	32
t.i.d.	17	(37%)	(90%)	(36%)	(36%)	(95%)	(34%)

*AUC is 0 to 12 hours for b.i.d. and 0 to 8 hours for t.i.d., therefore the C_{avg} is a better comparison of the exposures.

138 Geriatric Patients: The pharmacokinetics of amprenavir have not been studied in patients 139 over 65 years of age.

Gender: The pharmacokinetics of amprenavir do not differ between males and females.

Race: The pharmacokinetics of amprenavir do not differ between Blacks and non-Blacks.

142 Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS:

Drug Interactions.

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144 Amprenavir is metabolized in the liver by the cytochrome P450 enzyme system.

145 Amprenavir inhibits CYP3A4. Caution should be used when coadministering medications

that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that

are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9.

CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with amprenavir capsules and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of amprenavir on the AUC, C_{max}, and C_{min} are summarized in

152 Table 3 (effect of other drugs on amprenavir) and Table 4 (effect of amprenavir on other

drugs). For information regarding clinical recommendations, see PRECAUTIONS.

				% Change in A	Amprenavir Pha	armacokinetic
Co-	Dose of			Parameters*		
administered	Coadministered	Dose of			(90% CI)]
Drug	Drug	AGENERASE	ก	C _{max}	AUC	Cmin
	300 mg b.i.d.	900 mg b.i.d.		↑ 47	1€29	↑ 27
Abacavir	for 3 weeks	for 3 weeks	4	(↓ 15 to ↑ 154)	(↓18 to ↑103)	(↓ 46 to ↑ 197)
	500 mg b.i.d.	1200 mg b.i.d.		个15	个18	↑39
Clarithromycin	for 4 days	for 4 days	12	(个1 to 个31)	(个8 to 个29)	(个31 to 个47)
	800 mg t.i.d.	750 or 800 mg				
	for 2 weeks	t.i.d. for 2 weeks		18	↑ 33	↑ 25
Indinavir	(fasted)	(fasted)	9	(少 13 to 个 58)	(个2 to 个73)	(4 27 to ↑ 116)
	400 mg	1200 mg		₩16	↑31	·
Ketoconazole	single dose	single dose	12	(√ 25 to √ 6)	(个20 to 个42)	NA
	150 mg	600-mg		⇔	©	
Lamivudine	single dose	single dose	11	(↓ 17 to ↑ 9)	(↓ 15 to ↑ 14)	NA
	750 mg t.i.d.	750 or 800 mg				
	for 2 weeks	t.i.d. for 2 weeks		↓ 14	⇔	189
Nelfinavir	(fed)	(fed)	6	(√ 38 to ↑ 20)	(↓ 19 to ↑ 47)	(个52 to 个448)
	300 mg q.d.	1200 mg b.i.d.		0	↓ 15	↓ 15
Rifabutin	for 10 days	for 10 days	5	(1 √21 to 1 10)	(√ 28 to 0)	(√ 38 to ↑ 17)
	300 mg	1200 mg b.i.d.		↓ 70	↓82	↓ 92
Rifampin	q.d. for 4 days	for 4 days	11	(↓ 76 to ↓ 62)	(√ 84 to √ 78)	(1 95 to 1 89)
	800 mg t.i.d.	750 or 800 mg				·
	for 2 weeks	t.i.d. for 2 weeks		↓ 37	↓ 32	↓ 14
Saquinavir	(fed)	(fed)	7	(\$\sqrt{54}\ \to\$\$\sqrt{14})	(√ 49 to √ 9)	(√ 52 to ↑ 54)
-	300 mg	600 mg		⇔	13	
Zidovudine	single dose	single dose	12	(√5 to ↑24)	(√ 2 to ↑ 31)	NA .
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^{*}Based on total-drug concentrations.

¹⁵⁸ \uparrow = Increase; \downarrow = Decrease; \Leftrightarrow = No change (\uparrow or \downarrow <10%); NA = C_{min} not calculated for

¹⁵⁹ single-dose study.

Table 4: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir

				% Change in Pharmacokinetic Parameters of		
Co-	Dose of			Coadministered Drug		
administered	Coadministered	Dose of			(90% CI)	
Drug	Drug	AGENERASE	n	C _{max}	AUC	C _{min}
	500 mg b.i.d.	1200 mg b.i.d.		↓ 10	⇔	⇔ ·
Clarithromycin	for 4 days	for 4 days	12	(√ 24 to ↑ 7)	(↓ 17 to ↑ 11)	(少 13 to 个 20)
	400 mg	1200 mg		个19	↑ 44	
Ketoconazole	single dose	single dose	12	(个8 to 个33)	(个31 to 个59)	NA
	150 mg	600 mg		⇔	0	
Lamivudine	single dose	single dose	11	(少 17 to 个 3)	(↓ 11 to 0)	NA
	300 mg q.d.	1200 mg b.i.d.		个119	↑193	个271
Rifabutin	for 10 days	for 10 days	5	(个82 to 个164)	(个156 to 个235)	(个171 to 个409)
	300 mg	1200 mg b.i.d.		. ⇔	0	
Rifampin	q.d. for 4 days	for 4 days	11	(↓ 13 to ↑ 12)	(↓ 10 to ↑ 13)	ND
	300 mg	600 mg	1	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1 ↑31	
Zidovudine	single dose	single dose	12	(个14 to 个71)	(个19 to 个45)	NA

 \uparrow = Increase; \downarrow = Decrease; \Leftrightarrow = No change (\uparrow or \downarrow <10%); NA = C_{min} not calculated for

single-dose study; ND = Interaction cannot be determined as C_{min} was below the lower limit

165 of quantitation.

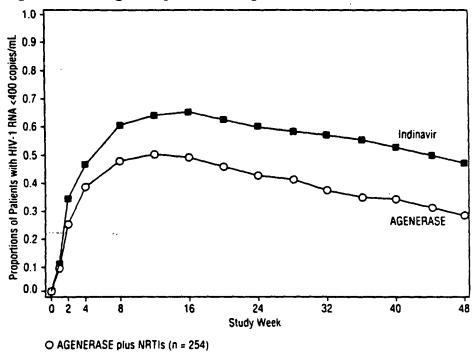
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): There was no effect of amprenavir on abacavir in subjects receiving both agents based on historical data.

HIV Protease Inhibitors: The effect of amprenavir on total drug concentrations of other HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C_{max} , AUC, and C_{min} were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and AUC were seen after the first dose. Saquinavir steady-state C_{max} , AUC, and C_{min} were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state C_{max} , AUC, and C_{min} were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

1//	ror information regarding clinical recommendations, see PRECAUTIONS: Drug
178	Interactions.
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180	INDICATIONS AND USAGE: AGENERASE (amprenavir) is indicated in combination
181	with other antiretroviral agents for the treatment of HIV-1 infection.
182	The following points should be considered when initiating therapy with
183	AGENERASE:
184	In a study of NRTI-experienced, protease inhibitor-naive patients,
185	AGENERASE was found to be significantly less effective than indinavir (see
186	Description of Clinical Studies).
187	Mild to moderate gastrointestinal adverse events led to discontinuation of
188	AGENERASE primarily during the first 12 weeks of therapy (see ADVERSE
189	REACTIONS).
190	There are no data on response to therapy with AGENERASE in protease
191	inhibitor-experienced patients.
192	Description of Clinical Studies: Therapy-Naive Adults: PROAB3001, a randomized,
193	double-blind, placebo-controlled, multicenter study, compared treatment with AGENERASE
194	Capsules (1200 mg twice daily) plus lamivudine (150 mg twice daily) plus zidovudine
195	(300 mg twice daily) versus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice
196	daily) in 232 patients. Through 24 weeks of therapy, 53% of patients assigned to
197	AGENERASE/zidovudine/lamivudine achieved HIV RNA <400 copies/mL. Through
198	week 48, the antiviral response was 41%. Through 24 weeks of therapy, 11% of patients
199	assigned to zidovudine/lamivudine achieved HIV RNA <400 copies/mL. Antiviral response
200	beyond week 24 is not interpretable because the majority of patients discontinued or change
201	their antiretroviral therapy.
202	NRTI-Experienced Adults: PROAB3006, a randomized, open-label multicenter study,
203	compared treatment with AGENERASE Capsules (1200 mg twice daily) plus NRTIs versus
204	indinavir (800 mg every 8 hours) plus NRTIs in 504 NRTI-experienced, protease
205	inhibitor-naive patients, median age 37 years (range 20 to 71 years), 72% Caucasian, 80%
206	male, with a median CD4 cell count of 404 cells/mm ³ (range 9 to 1706 cells/mm ³) and a
207	median plasma HIV-1 RNA level of 3.93 log ₁₀ copies/mL (range 2.60 to

7.01 log₁₀ copies/mL) at baseline. Through 48 weeks of therapy, the median CD4 cell count increase from baseline in the amprenavir group was significantly lower than in the indinavir group, 97 cells/mm³ versus 144 cells/mm³, respectively. There was also a significant difference in the proportions of patients with plasma HIV-1 RNA levels <400 copies/mL through 48 weeks (see Figure 1 and Table 5).

Figure 1: Virologic Response Through Week 48, PROAB3006*.*



Indinavir plus NRTIs (n = 250)

HIV-1 RNA status and reasons for discontinuation of randomized treatment at 48 weeks are summarized (Table 5).

^{*}Roche AMPLICOR HIV-1 MONITOR assay.

¹Discontinuations and missing data were considered as HIV-1 RNA ≥400 copies/mL.

Table 5: Outcomes of Randomized Treatment Through Week 48

(PROAB3006)

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	AGENERASE	Indinavir
Outcome	(n = 254)	(n = 250)
HIV RNA <400 copies/mL*	30%	49%
HIV RNA ≥400 copies/mL ^{1,‡}	38%	26%
Discontinued due to adverse events**	16%	12%
Discontinued due to other reasons:	16%	13%

^{*}Corresponds to rates at Week 48 in Figure 1.

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CONTRAINDICATIONS: Coadministration of AGENERASE is contraindicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 6.

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Table 6: Drugs That are Contraindicated with AGENERASE

Drug Class	Drugs Within Class That Are CONTRAINDICATED with AGENERASE
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hyponotics	Midazolam, triazolam

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Because of the potential toxicity from the large amount of the excipient propylene glycol contained in AGENERASE Oral Solution, that formulation is contraindicated in certain patient populations and should be used with caution in others. Consult the complete prescribing information for AGENERASE Oral Solution for full information.

[†]Virological failures at or before Week 48.

²Considered to be treatment failure in the analysis.

[§]Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations.

²²⁶ non-compliance, pregnancy, never treated, and other reasons.

237	AGENTIANSE is containaleated in patients with previously demonstrated chineany
240	significant hypersensitivity to any of the components of this product.
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242	WARNINGS: ALERT: Find out about medicines that should not be taken with
243	AGENERASE.
244	Serious and/or life-threatening drug interactions could occur between amprenavir
245	and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine.
246	Concentration monitoring of these agents is recommended if these agents are used
247	concomitantly with AGENERASE (see CONTRAINDICATIONS).
248	Rifampin should not be used in combination with amprenavir because it reduces plasma
249	concentrations and AUC of amprenavir by about 90%.
250	Concomitant use of AGENERASE and St. John's wort (hypericum perforatum) or products
251	containing St. John's wort is not recommended. Coadministration of protease inhibitors,
252	including AGENERASE, with St. John's wort is expected to substantially decrease protease
253	inhibitor concentrations and may result in suboptimal levels of amprenavir and lead to loss of
254	virologic response and possible resistance to AGENERASE or to the class of protease
255	inhibitors.
256	Concomitant use of AGENERASE with lovastatin or simvastatin is not recommended.
257	Caution should be exercised if HIV protease inhibitors, including AGENERASE, are used
258	concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the
259	CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including
260	rhabdomyolysis, may be increased when HIV protease inhibitors, including amprenavir. are
261	used in combination with these drugs.
262	Particular caution should be used when prescribing sildenafil in patients receiving
263	amprenavir. Coadministration of AGENERASE with sildenafil is expected to substantially
264	increase sildenafil concentrations and may result in an increase in sildenafil-associated
265	adverse events, including hypotension, visual changes, and priapism (see PRECAUTIONS:
266	Drug Interactions and Information for Patients, and the complete prescribing information for
267	sildenafil).
268	Because of the potential toxicity from the large amount of the excipient propylene glycol
269	contained in AGENERASE Oral Solution, that formulation is contraindicated in certain

270	patient populations and should be used with caution in others. Consult the complete
271	prescribing information for AGENERASE Oral Solution for full information.
272	Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have
273	occurred in patients treated with AGENERASE (see ADVERSE REACTIONS). Acute
274	hemolytic anemia has been reported in a patient treated with AGENERASE.
275	New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and
276	hyperglycemia have been reported during post-marketing surveillance in HIV-infected
277	patients receiving protease inhibitor therapy. Some patients required either initiation or dose
278	adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some
279	cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease
280	inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been
281	reported voluntarily during clinical practice, estimates of frequency cannot be made and
282	causal relationships between protease inhibitor therapy and these events have not been
283	established.
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285	PRECAUTIONS:
286	General: AGENERASE Capsules and AGENERASE Oral Solution are not
287	interchangeable on a milligram-per-milligram basis (see CLINICAL
288	PHARMACOLOGY: Pediatric Patients).
289	Amprenavir is a sulfonamide. The potential for cross-sensitivity between drugs in the
290	sulfonamide class and amprenavir is unknown. AGENERASE should be used with caution in
291	patients with a known sulfonamide allergy.
292	AGENERASE is principally metabolized by the liver; therefore caution should be
293	exercised when administering this drug to patients with hepatic impairment (see DOSAGE
294.	AND ADMINISTRATION).
295	Formulations of AGENERASE provide high daily doses of vitamin E (see Information for
296	Patients, DESCRIPTION, and DOSAGE AND ADMINISTRATION). The effects of
297	long-term, high-dose vitamin E administration in humans is not well characterized and has not
298	been specifically studied in HIV-infected individuals. High vitamin E doses may exacerbate
299	the blood coagulation defect of vitamin K deficiency caused by anticoagulant therapy or
300	malabsorption.

301	Patients with Hemophilia: There have been reports of spontaneous bleeding in patients with
302	hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII
303	was required. In many of the reported cases, treatment with protease inhibitors was continued
304	or restarted. A causal relationship between protease inhibitor therapy and these episodes has
305	not been established.
306	Fat Redistribution: Redistribution/accumulation of body fat, including central obesity,
307	dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and
308	"cushingoid appearance," have been observed in patients receiving protease inhibitors. The
309	mechanism and long-term consequences of these events are currently unknown. A causal
310	relationship has not been established.
311	Resistance/Cross-Resistance: Because the potential for HIV cross-resistance among protease
312	inhibitors has not been fully explored, it is unknown what effect amprenavir therapy will have
313	on the activity of subsequently administered protease inhibitors. It is also unknown what
314	effect previous treatment with other protease inhibitors will have on the activity of amprenavir
3 i š	(see MICROBIOLOGY).
316	Information for Patients: A statement to patients and health care providers is included on
317	the product's bottle label: ALERT: Find out about medicines that should NOT be taken
318	with AGENERASE. A Patient Package Insert (PPI) for AGENERASE Capsules is available
319	for patient information.
320	Patients treated with AGENERASE Capsules should be cautioned against switching to
321	AGENERASE Oral Solution because of the increased risk of adverse events from the large
322	amount of propylene glycol in AGENERASE Oral Solution. Please see the complete
323	prescribing information for AGENERASE Oral Solution for full information.
324	Patients should be informed that AGENERASE is not a cure for HIV infection and that
325	they may continue to develop opportunistic infections and other complications associated with
326	HIV disease. The long-term effects of AGENERASE (amprenavir) are unknown at this time.
327	Patients should be told that there are currently no data demonstrating that therapy with
328	AGENERASE can reduce the risk of transmitting HIV to others through sexual contact.
329	Patients should remain under the care of a physician while using AGENERASE. Patients
330	should be advised to take AGENERASE every day as prescribed. AGENERASE must always
331	be used in combination with other antiretroviral drugs. Patients should not alter the dose or

332	discondinate dictapy without consuming area physician in a dose is missed, panents should
333	take the dose as soon as possible and then return to their normal schedule. However, if a dose
334	is skipped, the patient should not double the next dose.
335	Patients should inform their doctor if they have a sulfa allergy. The potential for
336	cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown.
337	AGENERASE may interact with many drugs; therefore, patients should be advised to
338	report to their doctor the use of any other prescription, nonprescription medication, or herbal
339	products, particularly St. John's wort.
340	Patients taking antacids (or the buffered formulation of didanosine) should take
341	AGENERASE at least 1 hour before or after antacid (or the buffered formulation of
342	didanosine) use.
343	Patients receiving sildenafil should be advised that they may be at an increased risk of
344	sildenafil-associated adverse events, including hypotension, visual changes, and priapism, and
345	should promptly report any symptoms to their doctor.
346	Patients receiving hormonal contraceptives should be instructed that alternate contraceptive
347	measures should be used during therapy with AGENERASE.
348	High-fat meals may decrease the absorption of AGENERASE and should be avoided.
349	AGENERASE may be taken with meals of normal fat content.
350	Patients should be informed that redistribution or accumulation of body fat may occur in
351	patients receiving protease inhibitors and that the cause and long-term health effects of these
352	conditions are not known at this time.
353	Adult and pediatric patients should be advised not to take supplemental vitamin E since
354	the vitamin E content of AGENERASE Capsules and Oral Solution exceeds the Reference
355	Daily Intake (adults 30 IU, pediatrics approximately 10 IU).
356	Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and
357	CLINICAL PHARMACOLOGY: Drug Interactions.
358	AGENERASE is an inhibitor of cytochrome P450 3A4 metabolism and therefore
359	should not be administered concurrently with medications with narrow therapeutic
360	windows that are substrates of CYP3A4. There are other agents that may result in
361	serious and/or life-threatening drug interactions (see CONTRAINDICATIONS and
362	WARNINGS).

363 364

Table 7: Drugs That Should Not Be Coadministered with AGENERASE

Drug Class/Drug Name	Clinical Comment
Antihistamines:	CONTRAINDICATED due to potential for serious and/or
Astemizole, terfenadine	life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials:	May lead to loss of virologic response and possible resistance to
Rifampin	AGENERASE or to the class of protease inhibitors.
· · · · · · · · · · · · · · · · · · ·	CONTRAINDICATED due to potential for serious and/or
Ergot derivatives:	life-threatening reactions such as acute ergot toxicity
Dihydroergotamine, ergonovine,	characterized by peripheral vasospasm and ischemia of the
ergotamine, methylergonovine	extremities and other tissues.
GI motility agents:	CONTRAINDICATED due to potential for serious and/or
Cisapride	life-threatening reactions such as cardiac arrhythmias.
Herbal Products:	
St. John's wort (hypericum	May lead to loss of virologic response and possible resistance to
perforatum)	AGENERASE or to the class of protease inhibitors.
HMG Co-Reductase	
Inhibitors:	Potential for serious reactions such as risk of myopathy
Lovastatin, simvastatin	including rhabdomyolysis.
Neuroleptic:	CONTRAINDICATED due to potential for serious and/or life-
Pimozide	threatening reactions such as cardiac arrhythmias.
	CONTRAINDICATED due to potential for serious and/or life-
Sedative/hypnotics:	threatening reactions such as prolonged or increased sedation or
Midazolam, triazolam	respiratory depression.

365 366

Table 8: Established and Other Potentially Significant Drug Interactions:

Alteration in Dose or Regimen May be Recommended Based on Drug Interaction

Studies or Predicted Interaction

368

367

Effect on Concentration of Amprenavir or Concomitant Concomitant Drug Class: Drug Name Drug **Clinical Comment** HIV-Antiviral Agents Non-nucleoside Reverse Transcriptase Inhibitors: Appropriate doses of the combinations with respect to safety and efficacy have not been established. Efavirenz, nevirapine **↓**Amprenavir Non-nucleoside Reverse Transcriptase Inhibitor: Appropriate doses of the combination with respect to safety and efficacy have not been established Delavirdine **TAmprenavir** Nucleoside Reverse Transcriptase Inhibitor: Didanosine (buffered Take AGENERASE at least 1 hour before or after

Communication and the		the buffered formulation of didanosine.
formulation only)	↓Amprenavir	the buffered formulation of didanosine.
1	†Amprenavir	
	Amprenavir's	·
HIV-Protease Inhibitors:	effect on other	
Indinavir*,	protease inhibitors	
lopinavir/ritonavir,	is not well	Appropriate doses of the combinations with respect
nelfinavir*, ritonavir	established.	to safety and efficacy have not been established.
	↓Amprenavir	
	Amprenavir's	
	effect on	
HIV-Protease Inhibitor:	saquinavir is not	Appropriate doses of the combination with respect
Saquinavir*	well established.	to safety and efficacy have not been established.
	Othe	er Agents
- -		Take AGENERASE at least 1 hour before or after
Antacids	↓Amprenavir	antacids.
		Caution is warranted and therapeutic concentration
Antiarrbythmics:		monitoring is recommended for antiarrhythmics
Amiodarone, lidocaine		when coadministered with AGENERASE, if
(systemic), and quinidine	†Antiarrhythmics	available.
		Use with caution. Increased bepridil exposure may
Antiarrhythmic:	}	be associated with life-threatening reactions such
Bepridil	†Bepridil	as cardiac arrhythmias.
		Concentrations of warfarin may be affected. It is
Anticoagulant:		recommended that INR (international normalized
Warfarin]	ratio) be monitored:
		Use with caution. AGENERASE may be less
Anticonvulsants:	İ	effective due to decreased amprenavir plasma
Carbamazepine,		concentrations in patients taking these agents
phenobarbital, phenytoin	↓Amprenavir	concomitantly.
		Increase monitoring for adverse events due to
		ketoconazole or itraconazole. Dose reduction of
Antifungals:		ketoconazole or itraconazole may be needed for
Ketoconazole,	↑Ketoconazole	patients receiving more than 400 mg ketoconazole
itraconazole	Titraconazole	or itraconazole per day.
		A dosage reduction of rifabutin to at least half the
	<u>}</u>	recommended dose is required when
_		AGENERASE and rifabutin are coadministered.*
		A complete blood count should be performed
	TRifabutin and	weekly and as clinically indicated in order to
Antimycobacterial:	rifabutin	monitor for neutropenia in patients receiving
Rifabutin*	metabolite	amprenavir and rifabutin.
Benzodiazepines:	1	
Alprazolam, clorazepate,	}	Clinical significance is unknown; however, a
diazepam, flurazepam	†Benzodiazepines	decrease in benzodiazepine dose may be needed.
Calcium Channel		
Blockers:		- 116
Diltiazem, felodipine,		

nifedipine, nicardipine, nimodipine, verapamil,		
amlodipine, nisoldipine,	†Calcium channel	Caution is warranted and clinical monitoring of
isradipine	blockers	patients is recommended.
	** .* .	Use with caution. AGENERASE may be less
(·	effective due to decreased amprenavir plasma
Corticosteroid:		concentrations in patients taking these agents
Dexamethasone	↓Amprenavir	concomitantly.
Erectile Dysfunction		Use with caution at reduced doses of 25 mg every
Agent:		48 hours with increased monitoring for adverse
Sildenafil	†Sildenafil	events.
		Use lowest possible dose of atorvastatin or
		cerivastatin with careful monitoring or consider
HMG-CoA Reductase		other HMG-CoA reductase inhibitors such as
Inhibitors:	TAtorvastatin,	pravastatin or fluvastatin in combination with
Atorvastatin, cerivastatin	†Cerivastatin	AGENERASE.
Immunosuppressants:		Therapeutic concentration monitoring is
Cyclosporine, tacrolimus,	↑lmmunosup-	recommended for immunosuppressant agents when
rapamycin	pressants	coadministered with AGENERASE.
		Alternative or additional contraceptive measures
1	Effect on ethinyl	should be used when estrogen-based oral
Oral Contraceptive:	estradiol is not	contraceptives and AGENERASE are
Ethinyl estradiol	known.	coadministered.
Tricyclic		Therapeutic concentration monitoring is
Antidepressants:		recommended for tricyclic antidepressants when
Amitriptyline, imipramine	†Tricyclics	coadministered with AGENERASE.

^{*}See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 3 and 4.

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Carcinogenesis and Mutagenesis: Long-term carcinogenicity studies of amprenavir in rodents are in progress. Amprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

Fertility: The effects of amprenavir on fertility and general reproductive performance were investigated in male rats (treated for 28 days before mating at doses producing up to twice the expected clinical exposure based on AUC comparisons) and female rats (treated for 15 days before mating through day 17 of gestation at doses producing up to 2 times the expected clinical exposure). Amprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats. The reproductive performance of the F1 generation born to female rats given amprenavir was not different from control animals.

383	Pregnancy and Reproduction: Pregnancy Category C. Embryo/tetal development studies
384	were conducted in rats (dosed from 15 days before pairing to day 17 of gestation) and rabbits
385	(dosed from day 8 to day 20 of gestation). In pregnant rabbits, amprenavir administration was
386	associated with abortions and an increased incidence of 3 minor skeletal variations resulting
387	from deficient ossification of the femur, humerus trochlea, and humerus. Systemic exposure at
388	the highest tested dose was approximately one twentieth of the exposure seen at the
389	recommended human dose. In rat fetuses, thymic elongation and incomplete ossification of
390	bones were attributed to amprenavir. Both findings were seen at systemic exposures that were
391	one half of that associated with the recommended human dose.
392	Pre- and post-natal developmental studies were performed in rats dosed from day 7 of
393	gestation to day 22 of lactation. Reduced body weights (10% to 20%) were observed in the
394	offspring. The systemic exposure associated with this finding was approximately twice the
395	exposure in humans following administration of the recommended human dose. The
396	subsequent development of these offspring, including fertility and reproductive performance,
397	was not affected by the maternal administration of amprenavir.
398	There are no adequate and well-controlled studies in pregnant women.
399	AGENERASE should be used during pregnancy only if the potential benefit justifies
400	the potential risk to the fetus.
401	AGENERASE Oral Solution is contraindicated during pregnancy due to the
402	potential risk of toxicity to the fetus from the high propylene glycol content.
403	Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of
404	pregnant women exposed to AGENERASE, an Antiretroviral Pregnancy Registry has
405	been established. Physicians are encouraged to register patients by calling 1-800-258-
406	4263.
407	Nursing Mothers: The Centers for Disease Control and Prevention recommend that
408	HIV-infected mothers not breastfeed their infants to avoid risking postnatal
409	transmission of HIV. Although it is not known if amprenavir is excreted in human milk,
410 -	amprenavir is secreted into the milk of lactating rats. Because of both the potential for HIV
411	transmission and the potential for serious adverse reactions in nursing infants, mothers
412	should be instructed not to breastfeed if they are receiving AGENERASE.

413	a editative ose. I wo fidilities they one patients aged 4 and above have received amplehavir as
414	single or multiple doses in studies. An adverse event profile similar to that seen in adults was
415	seen in pediatric patients.
416	AGENERASE Capsules have not been evaluated in pediatric patients below the age of
417	4 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).
418	AGENERASE Oral Solution is contraindicated in infants and children below the age of
419	4 years due to the potential risk of toxicity from the large amount of the excipient propylene
420	glycol. Please see the complete prescribing information for AGENERASE Oral Solution for
421	full information.
422	Geriatric Use: Clinical studies of AGENERASE did not include sufficient numbers of
423	patients aged 65 and over to determine whether they respond differently from younger adults.
424	In general, dose selection for an elderly patient should be cautious, reflecting the greater
425	frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other
426	drug therapy.
427-	
428	ADVERSE REACTIONS: In clinical studies, adverse events leading to amprenavir
429	discontinuation occurred primarily during the first 12 weeks of therapy, and were mostly due
430	to gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain/discomfort). which
431	were mild to moderate in severity.
432	Skin rash occurred in 22% of patients treated with amprenavir in studies PROAB3001 and
433	PROAB3006. Rashes were usually maculopapular and of mild or moderate intensity, some
434	with pruritus. Rashes had a median onset of 11 days after amprenavir initiation and a median
435	duration of 10 days. Skin rashes led to amprenavir discontinuation in approximately 3% of
436	patients. In some patients with mild or moderate rash, amprenavir dosing was often continued
437	without interruption; if interrupted, reintroduction of amprenavir generally did not result in
438	rash recurrence.
439	Severe or life-threatening rash (Grade 3 or 4), including cases of Stevens-Johnson
440	syndrome, occurred in approximately 1% of recipients of AGENERASE (see
441	WARNINGS). Amprenavir therapy should be discontinued for severe or
442	life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

Table 9: Selected Clinical Adverse Events of All Grades Reported in >5% of Adult
Patients

·····	PROAB3001			PROAB3006		
	Therapy-Naive Patients		NRTI-Experienced Patients			
	AGENERASE*/					
	Lamivudine/	Lamivudine/	AGENERASE*/			
	Zidovudine	Zidovudine	NRTI	Indinavir/NRTI		
Adverse Event	(n = 113)	(n = 109)	(n = 245)	(n = 241)		
Digestive						
Nausea	74%	50%	43%	35%		
Vomiting	34%	17%	24%	20%		
Diarrhea or loose stools	39%	35%	60%	41%		
Taste disorders	10%	6%	2%	8%		
Skin .						
Rash	27%	6%	20%	15%		
Nervous						
Paresthesia, oral/perioral	26%	6%	31%	2%		
Paresthesia, peripheral	10%	4%	14%	10%		
Psychiatric						
Depressive or mood disorders	16%	4%	9%	13%		

Among amprenavir-treated patients in Phase 3 studies, 2 patients developed de novo diabetes mellitus, 1 patient developed a dorsocervical fat enlargement (buffalo hump), and 9 patients developed fat redistribution.

- --449

Table 10: Selected Laboratory Abnormalities of All Grades Reported in ≥5% of Adult Patients

	PROAB3001		PROAB3006	
	Therapy-Nai	Therapy-Naive Patients		enced Patients
	AGENERASE/			
	Lamivudine/	Lamivudine/	AGENERASE	
Laboratory Abnormality	Zidovudine	Zidovudine	/NRTI	Indinavir/NRTI
(non-fasting specimens)	(n = 111)	(n = 108)	(n = 237)	(n = 239)
Hyperglycemia (>116 mg/dL)	45%	31%	53%	58%
Hypertriglyceridemia				
(>213 mg/dL)	41%	27%	56%	52%
Hypercholesterolemia				
(>283 mg/dL)	7%	3%	13%	15%

453

In studies PROAB3001 and PROAB3006, no increased frequency of Grade 3 or 4 AST,

ALT, amylase, or bilirubin elevations was seen compared to controls.

Pediatric Patients: An adverse event profile similar to that seen in adults was seen in

457 pediatric patients.

458

459

460

461

462

OVERDOSAGE: There is no known antidote for AGENERASE. It is not known whether amprenavir can be removed by peritoneal dialysis or hemodialysis. If overdosage occurs, the patient should be monitored for evidence of toxicity and standard supportive treatment applied as necessary.

463

466

467

468

DOSAGE AND ADMINISTRATION: AGENERASE may be taken with or without food;

however, a high-fat meal decreases the absorption of amprenavir and should be avoided (see

CLINICAL PHARMACOLOGY: Effects of Food on Oral Absorption). Adult and pediatric

patients should be advised not to take supplemental vitamin E since the vitamin E

content of AGENERASE Capsules exceeds the Reference Daily Intake (adults 30 IU,

pediatrics approximately 10 IU) (see DESCRIPTION).

470	Addits: The recommended oral dose of AGENERASE Capsules for addits is 1200 mg
471	(eight 150-mg capsules) twice daily in combination with other antiretroviral agents.
472	Pediatric Patients: For adolescents (13 to 16 years), the recommended oral dose of
473	AGENERASE Capsules is 1200 mg (eight 150-mg capsules) twice daily in combination with
474	other antiretroviral agents. For patients between 4 and 12 years of age or for patients 13 to
475	16 years of age with weight of <50 kg, the recommended oral dose of AGENERASE
476	Capsules is 20 mg/kg twice daily or 15 mg/kg 3 times daily (to a maximum daily dose of
477	2400 mg) in combination with other antiretroviral agents.
478	Before using AGENERASE Oral Solution, the complete prescribing information should
479	be consulted.
480	AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on
481	a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY).
482	Patients with Hepatic Impairment: AGENERASE Capsules should be used with caution in
483	patients with moderate or severe hepatic impairment. Patients with a Child-Pugh score
484	ranging from 5 to 8 should receive a reduced dose of AGENERASE Capsules of 450 mg
485	twice daily, and patients with a Child-Pugh score ranging from 9 to 12 should receive a
486	reduced dose of AGENERASE Capsules of 300 mg twice daily (see CLINICAL
487	PHARMACOLOGY: Hepatic Insufficiency).
488	- -
489	HOW SUPPLIED: AGENERASE Capsules, 50 mg, are oblong, opaque, off-white to
490	cream-colored soft gelatin capsules printed with "GX CC1" on one side.
491	Bottles of 480 with child-resistant closures (NDC 0173-0679-00).
^492	AGENERASE Capsules, 150 mg, are oblong, opaque, off-white to cream-colored soft
493	gelatin capsules printed with "GX CC2" on one side.
494	Bottles of 240 with child-resistant closures (NDC 0173-0672-00).
495	Store at controlled room temperature of 25°C (77°F) (see USP).
496	
497	AGENERASE Capsules are manufactured by
498	R.P. Scherer
499	Beinheim, France
500	for
	· ·

501		Licensed from
502	GlaxoWellcome	VERTEX
503	Glaxo Wellcome Inc.	Vertex Pharmaceuticals Incorporated
504	Research Triangle Park, NC 27709	Cambridge, MA 02139
505		
506	AGENERASE is a registered trademan	rk of the Glaxo Wellcome group of companies.
507		
508	US Patent Nos. 5,585,397; 5,723,490;	and 5,646,180
509		
510	©2001, Glaxo Wellcome Inc. All righ	ts reserved.
511		
512	Date of Issue RL-no.	
513		
514	PHARMACIST-DETACH HE	RE AND GIVE INSTRUCTIONS TO PATIENT
515		
516	_	
517		
518	PATI	ENT INFORMATION
519		
520	AGENERASE® (amprenavir) Caps	ules
521		
522	ALERT: Find out about medicines	that should not be taken with AGENERASE. Please
523	also read the section "MEDICINES Y	OU SHOULD NOT TAKE WITH AGENERASE."
524		
525	Please read this information before yo	u start taking AGENERASE (pronounced ah-GEN-er-
526	ase) Capsules, and re-read it each time	you receive your prescription, just in case something
527	has changed. Remember that this info	rmation does not take the place of careful discussions
528	with your doctor when you start this n	nedication and at checkups. You should not change or
529	stop your anti-HIV treatment without	first talking with your doctor. You should tell your

530	doctor about any drug you are taking or planning to take because taking AGENERASE
531	Capsules with some medications can result in serious or life-threatening problems.
532	
533	You should not switch from AGENERASE Capsules to AGENERASE Oral Solution
534	without talking with your doctor.
535	
536	What are AGENERASE Capsules?
537	AGENERASE Capsules are a medication used to treat HIV infection. HIV is the virus that
538	causes AIDS (acquired immune deficiency syndrome). AGENERASE Capsules are taken by
539	mouth as soft gel capsules. AGENERASE belongs to a class of anti-HIV medicines called
540	protease inhibitors.
541	
542	How do AGENERASE Capsules work?
543	AGENERASE Capsules are used only in combination with other anti-HIV medicines. When
544	used in combination therapy, AGENERASE Capsules may help lower the amount of HIV
545	found in your blood, raise CD4 (T) cell count, and keep your immune system as healthy as
546	possible so that it can help fight infection. However, AGENERASE Capsules do not have
547	these effects in all patients.
548	
549	What are the side effects of AGENERASE Capsules?
550	Common side effects of AGENERASE Capsules are nausea, vomiting, diarrhea, rash, and a
551	tingling sensation around the mouth. Severe or life-threatening rash has been reported.
552	
553	Contact your doctor if you have nausea, vomiting, diarrhea, or rash. Your doctor may be able
554	to help you manage these symptoms. Your doctor will advise you whether your symptoms car
555	be managed on therapy or whether AGENERASE Capsules should be stopped.
556	
557	This list of side effects is not complete. Your doctor or pharmacist can discuss with you a
558	more complete list of possible side effects with AGENERASE Capsules. Talk to your doctor
559	promptly about any side effects you have.
560	

561	How should I take AGENERASE Capsules?
562	Take AGENERASE Capsules exactly as your doctor prescribes them. The usual dosage for
563	adults and adolescents (at least 13 years of age) is eight 150-mg soft gel capsules twice a day
564	(morning and night), in combination with other anti-HIV medicines.
565	
566	AGENERASE Capsules can be taken with or without food. However, you should not take
567	AGENERASE with a high-fat meal because this could reduce the effectiveness of
56 8	AGENERASE Capsules.
569	
570	What should I do if I miss a dose of AGENERASE Capsules?
571	To help make sure that your anti-HIV therapy is as effective as possible, be very careful to
572	take all of your medication exactly as your doctor prescribed it and do not skip any doses.
573	
574	If you miss a dose of AGENERASE Capsules by more than 4 hours, wait and take the next
575	dose at the regularly scheduled time. However, if you miss a dose by fewer than 4 hours, take
576	your missed dose immediately. Then take your next dose at the regularly scheduled time. Do
577	not take more or less than your prescribed dose of AGENERASE Capsules at any one time.
578	
579	When your supply of AGENERASE Capsules or other anti-HIV drugs starts to run low,
580	arrange to get more from your doctor or pharmacy. It is very important that you take anti-HIV
581	drugs as prescribed by your doctor because the amount of virus in your blood may increase if
582	one or more of the drugs is stopped, even for a short time.
583	
584	Can AGENERASE Capsules be taken with other medications?
585	Protease inhibitors, including AGENERASE, may interact with other drugs, including those
586	you take without a prescription. Before you take AGENERASE, tell your doctor about any
587	drugs that you are taking or planning to take, including nonprescription drugs.
588	
589	MEDICINES YOU SHOULD NOT TAKE WITH AGENERASE
590	• You should not take any of the following medications with AGENERASE Capsules
591	because serious or life-threatening problems could occur.*

592		HALCION (triazolam)	PROPULSID* (cisapride)		
593		HISMANAL [®] (astemizole)	VERSED [®] (midazolam)		
594		Ergot medications (CAFERGOT® and others)	VASCOR® (bepridil)		
595		ORAP® (pimozide)	SELDANE® (terfenadine)		
596					
597	•	You should also not take rifampin with AGE	NERASE Capsules because this drug		
598		reduces the effectiveness of AGENERASE. Rifampin is also known as: RIFADIN®,			
599		RIFAMATE®, RIFATER®, and RIMACTANE	€.		
600					
601	•	Taking AGENERASE with St. John's Wort (hy	pericum perforatum, a nonprescription		
602		herbal product) or products containing St. John	's Wort is not recommended. Talk with		
603	-	your doctor if you are taking or are planning to	take St. John's Wort because St. John's		
604		Wort may reduce the effect of AGENERASE.	•		
605					
606	•	It is not recommended that you take AGENER	ASE with the cholesterol-lowering drugs		
607		MEVACOR® (lovastatin) or ZOCOR® (simvastatin) because of the possible drug			
608		interactions. There is also an increased risk of drug interactions between AGENERASE			
609		and LIPITOR® (atorvastatin), and BAYCOL®	(cerivastatin). Talk to your doctor if you are		
610		taking or are planning to take these or other dra	igs for lowering cholesterol.		
611		-			
612	M	edicines That Require Dose Adjustments or S	pecial Attention From Your Doctor		
613	•	Serious and/or life-threatening drug interac	tions can also occur if you take		
614		AGENERASE Capsules with any of the following	owing drugs.* If you need to take any of		
615		these drugs, your doctor may closely monitor t	he amount of drug in your blood to		
616		minimize potential problems.			
617		CORDARONE® (amiodarone)			
618		Phenobarbital			
619		TEGRETOL [®] , CARBATROL [®] (carbamazepir	ne)		
620		DILANTIN® (phenytoin)			
621		Lidocaine			
622		COUMADIN® (warfarin)			

AGENERASE[®] (amprenavir) Capsules

623		(quinidine) QUINAGLUTE®, CARDIOQUIN®, QUINIDEX®
624		Antidepressants such as ELAVIL® (amitriptyline), NORPRAMIN® (desipramine),
625		PAMELOR® (nortriptyline), TOFRANIL® (imipramine)
626		_
627	•	Tell your doctor about any drugs that you are taking or planning to take, including
628		nonprescription drugs.
629		
630	•	Before you take VIAGRA® (sildenafil) with AGENERASE, talk to your doctor about
631		possible drug interactions and side effects. If you take VIAGRA and AGENERASE
632		together, you may be at increased risk of side effects of VIAGRA such as low blood
633		pressure, visual changes, and penile erection lasting more than 4 hours. If an erection last
634		longer than 4 hours, you should seek immediate medical assistance to avoid permanent
635		damage to your penis. Your doctor can explain these symptoms to you.
636		
637	•	If you use birth control pills, talk to your doctor about choosing a different type of
638		contraceptive, since AGENERASE may reduce the effectiveness of some birth control
639		pills.
640		
641	•	Because AGENERASE Capsules and Oral Solution contain large amounts of vitamin E,
642		you should not take additional vitamin E while taking AGENERASE.
643		
644	•	Special considerations:*
645		If you take AGENERASE Capsules with MYCOBUTIN® (rifabutin), your doctor will
646		lower the dose of MYCOBUTIN.
647		
648		If you take AGENERASE Capsules with VIDEX® (didanosine, ddl) (buffered
649		formulation), take them at least 1 hour apart.
650		
651		. If you take AGENERASE Capsules with antacids, take them at least 1 hour apart.
652		
653	Ď	o AGENERASE Capsules cure HIV infection or AIDS?

654	AGENERASE Capsules do not cure HIV infection or AIDS. At this time we do not know if
655	AGENERASE will help you live longer or have fewer of the medical problems (opportunistic
656	infections) that are associated with HIV infection or AIDS. Because of this, you must be sure
657	to be seen regularly by your healthcare professional.
658	
659	Do AGENERASE Capsules reduce the risk of passing HIV to others?
660	No. AGENERASE Capsules, as well as other anti-HIV medications, have not been shown to
661	reduce the risk of passing HIV to others through sexual contact or blood contamination.
662	Continue to practice safe sex and do not use or share dirty needles.
663	
664	Who should not take AGENERASE Capsules?
6 65	Do not take AGENERASE Capsules if you have had a serious allergic reaction to
666	AGENERASE or any of its ingredients. If you have liver disease, your dosage of
667	AGENERASE may have to be adjusted.
668	
669	If you are allergic to sulfa drugs, you should inform your doctor.
670	
671	Can children take AGENERASE Capsules?
672	Children from 4 to 12 years of age can take AGENERASE Capsules. Your doctor will tell
673	you if the oral solution or capsule is best for your child. Your child's doctor will decide the
674	right dose based on your child's weight and age. AGENERASE Oral Solution should not be
675	used in infants and children below 4 years of age.
676	
677	Can pregnant women and nursing mothers take AGENERASE?
678	AGENERASE Capsules have not been studied in pregnant women and the risk to the unborn
679	child is not known. Talk to your doctor if you are pregnant or if you become pregnant while
680	taking AGENERASE.
681	
682	AGENERASE Oral Solution should not be used in pregnant women.
683	

684	Mothers with HIV should not breastfeed their	r infants because HIV in the breast milk can	
685	infect the infant.	•	
686	•		
687	What other medical conditions should I d	iscuss with my doctor?	
688	Talk to your doctor if you are pregnant or if you become pregnant while you are taking		
689	AGENERASE.		
690			
691	Also talk to your doctor if you have hemoph	ilia or problems with your liver or kidneys.	
692			
693	How should I store AGENERASE Capsul	es?	
694	AGENERASE Capsules should be stored at	room temperature and should not be refrigerated.	
695			
696	Other information:		
697	This medication is prescribed for a particular condition. Do not use it for any other condition		
698	or give it to anybody else. Keep AGENERASE Capsules and all medicines out of the reach of		
699	children.		
700			
701	Ask a healthcare professional any questions	you may have about AGENERASE.	
702			
703	AGENERASE is a registered trademark of t	he Glaxo Wellcome group of companies.	
704			
705	*The brands listed are trademarks of their re	espective owners and are not trademarks of the	
706	Glaxo Wellcome group of companies. The makers of these brands are not affiliated with and		
707	do not endorse Glaxo Wellcome or its produ	acts.	
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712	Glaxo Wellcome Inc.	Vertex Pharmaceuticals Incorporated	
713	Research Triangle Park NC 27709	Cambridge, MA 02139	

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716 Date of Issue

RL-no.

AGENERASE®

- 3 (amprenavir)
- 4 Oral Solution

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PATIENT INFORMATION INCLUDED

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Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CONTRAINDICATIONS AND WARNINGS).

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

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DESCRIPTION: AGENERASE (amprenavir) is an inhibitor of the human

immunodeficiency virus (HIV) protease. The chemical name of amprenavir is (3S)-

tetrahydro-3-furyl N-[(1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-

hydroxypropyl]carbamate. Amprenavir is a single stereoisomer with the (3S)(1S,2R)

20 configuration. It has a molecular formula of C₂₅H₃₅N₃O₆S and a molecular weight of

21 505.64. It has the following structural formula:

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AGENERASE® (amprenavir) Oral Solution

Amprenavir is a white to cream-colored solid with a solubility of approximately 25 0.04 mg/mL in water at 25°C. 26 AGENERASE Oral Solution is for oral administration. One milliliter (1 mL) of 27 28 AGENERASE Oral Solution contains 15 mg of amprenavir in solution and the inactive ingredients acesulfame potassium, artificial grape bubblegum flavor, citric acid 29 30 (anhydrous), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol. natural peppermint flavor, polyethylene glycol 400 (PEG 400) (170 mg), propylene glycol 31 (550 mg), saccharin sodium, sodium chloride, and sodium citrate (dihydrate). Solutions of 32 sodium hydroxide and/or diluted hydrochloric acid may have been added to adjust pH. 33 34 Each mL of AGENERASE Oral Solution contains 46 IU vitamin E in the form of TPGS. Propylene glycol is in the formulation to achieve adequate solubility of amprenavir. The 35 recommended daily dose of AGENERASE Oral Solution of 22.5 mg/kg twice daily 36 corresponds to a propylene glycol intake of 1650 mg/kg per day. Acceptable intake of 37 propylene glycol for pharmaceuticals has not been established. 38 39 40 MICROBIOLOGY: 41 Mechanism of Action: Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and 42 43 gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles. 44 Antiviral Activity in Vitro: The in vitro antiviral activity of amprenavir was evaluated 45 against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-46 47 4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory 48 concentration (IC₅₀) of amprenavir ranged from 0.012 to 0.08 µM in acutely infected cells 49 and was 0.41 µM in chronically infected cells (1 µM = 0.50 mcg/mL). Amprenavir 50 exhibited synergistic anti-HIV-1 activity in combination with abacavir, zidovudine, 51 didanosine, or saquinavir, and additive anti-HIV-1 activity in combination with indinavir, 52 nelfinavir, and ritonavir in vitro. These drug combinations have not been adequately studied in humans. The relationship between in vitro anti-HIV-1 activity of amprenavir and 53 54 the inhibition of HIV-1 replication in humans has not been defined.

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AGENERASE® (amprenavir) Oral Solution

55	Resistance: HIV-1 isolates with a decreased susceptibility to amprenavir have been
56	selected in vitro and obtained from patients treated with amprenavir. Genotypic analysis of
57	isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene
58	resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V,
59	I54L/M, and I84V as well as mutations in the p7/p1 and p1/p6 gag cleavage sites.
60	Phenotypic analysis of HIV-1 isolates from 21 nucleoside reverse transcriptase inhibitor-
61	(NRTI-) experienced, protease inhibitor-naive patients treated with amprenavir in
62	combination with NRTIs for 16 to 48 weeks identified isolates from 15 patients who
63	exhibited a 4- to 17-fold decrease in susceptibility to amprenavir in vitro compared to
64	wild-type virus. Clinical isolates that exhibited a decrease in amprenavir susceptibility
65	harbored one or more amprenavir-associated mutations. The clinical relevance of the
66	genotypic and phenotypic changes associated with amprenavir therapy is under evaluation
67	Cross-Resistance: Varying degrees of HIV-1 cross-resistance among protease inhibitors
68	have been observed. Five of 15 amprenavir-resistant isolates exhibited 4- to 8-fold
69	decrease in susceptibility to ritonavir. However, amprenavir-resistant isolates were
70	susceptible to either indinavir or saquinavir.
71	
72	CLINICAL PHARMACOLOGY:
73	Pharmacokinetics in Adults: The pharmacokinetic properties of amprenavir have been
74	studied in asymptomatic, HTV-infected adult patients after administration of single oral
75	doses of 150 to 1200 mg and multiple oral doses of 300 to 1200 mg twice daily.
76	Absorption and Bioavailability: Amprenavir was rapidly absorbed after oral
77	administration in HIV-1-infected patients with a time to peak concentration (t _{max}) typically
78	between 1 and 2 hours after a single oral dose. The absolute oral bioavailability of
79	amprenavir in humans has not been established.
80	Increases in the area under the plasma concentration versus time curve (AUC) after
81	single oral doses between 150 and 1200 mg were slightly greater than dose proportional.
82	Increases in AUC were dose proportional after 3 weeks of dosing with doses from 300 to
83	1200 mg twice daily. The pharmacokinetic parameters after administration of amprenavir
84	1200 mg b.i.d. for 3 weeks to HIV-infected subjects are shown in Table 1.

AGENERASE® (amprenavir) Oral Solution

Table 1: Average (%CV) Pharmacokinetic Parameters After 1200 mg b.i.d. of Amprenavir Capsules (n = 54)

Cmax	t _{max}	AUC ₀₋₁₂	Cavg	Cmin	CL/F
(mcg/mL)	(hours)	(mcg•h/mL)	(mcg/mL)	(mcg/mL)	(mL/min/kg)
7.66 (54%)	1.0 (42%)	17.7 (47%)	1.48 (47%)	0.32 (77%)	19.5 (46%)

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The relative bioavailability of AGENERASE Capsules and Oral Solution was assessed in healthy adults. AGENERASE Oral Solution was 14% less bioavailable compared to the capsules.

92 Effects of Food on Oral Absorption: The relative bioavailability of AGENERASE

Capsules was assessed in the fasting and fed states in healthy volunteers (standardized

high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate).

Administration of a single 1200-mg dose of amprenavir in the fed state compared to the

fasted state was associated with changes in C_{max} (fed: 6.18 \pm 2.92 mcg/mL, fasted:

97 9.72 \pm 2.75 mcg/mL), t_{max} (fed: 1.51 \pm 0.68, fasted: 1.05 \pm 0.63), and AUC_{0-\infty} (fed:

22.06 \pm 11.6 mcg•h/mL, fasted: 28.05 \pm 10.1 mcg•h/mL). AGENERASE may be taken

with or without food, but should not be taken with a high-fat meal (see DOSAGE AND

100 ADMINISTRATION).

Distribution: The apparent volume of distribution (V₂/F) is approximately 430 L in healthy adult subjects. In vitro binding is approximately 90% to plasma proteins. The high affinity binding protein for amprenavir is alpha₁-acid glycoprotein (AAG). The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism: Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

AGENERASE Oral Solution contains a large amount of propylene glycol, which is hepatically metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway.

Alcohol dehydrogenase (ADH) is present in the human fetal liver at 2 months of

gestational age, but at only 3% of adult activity. Although the data are limited, it appears

114	that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that
115	observed in adults. Additionally, certain patient groups (females, Asians, Eskimos, Native
116	Americans) may be at increased risk of propylene glycol-associated adverse events due to
117	diminished ability to metabolize propylene glycol (see CLINICAL PHARMACOLOGY:
118	Special Populations: Gender and Race).
119	Elimination: Excretion of unchanged amprenavir in urine and feces is minimal.
120	Approximately 14% and 75% of an administered single dose of ¹⁴ C-amprenavir can be
121	accounted for as radiocarbon in urine and feces, respectively. Two metabolites accounted
122	for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of
123	amprenavir ranged from 7.1 to 10.6 hours.
124	Special Populations: Hepatic Insufficiency: AGENERASE Oral Solution is
125	contraindicated in patients with hepatic failure.
126	Patients with hepatic impairment are at increased risk of propylene glycol-associated
127	adverse events (see WARNINGS). AGENERASE Oral Solution should be used with
128	caution in patients with hepatic impairment. AGENERASE Capsules have been studied in
129	adult patients with impaired hepatic function using a single 600-mg oral dose. The AUC ₀ .
130	was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•h/mL)
131	compared with healthy volunteers (12.00 ± 4.38 mcg•h/mL). The AUC _{0-∞} and C _{max} were
132	significantly greater in patients with severe cirrhosis (AUC _{0-∞} : 38.66 ± 16.08 mcg•h/mL;
133	C_{max} : 9.43 ± 2.61 mcg/mL) compared with healthy volunteers (AUC _{0-∞} :
134	12.00 ± 4.38 mcg+h/mL; C_{max} : 4.90 ± 1.39 mcg/mL). Patients with impaired hepatic
135	function require dosage adjustment (see DOSAGE AND ADMINISTRATION).
136	Renal Insufficiency: AGENERASE Oral Solution is contraindicated in patients with
137	renal failure.
138	Patients with renal impairment are at increased risk of propylene glycol-associated
139	adverse events. Additionally, because metabolites of the excipient propylene glycol in
140	AGENERASE Oral Solution may alter acid-base balance, patients with renal impairment
141	should be monitored for potential adverse events (see WARNINGS). AGENERASE Oral
142	Solution should be used with coution in nationts with rangl impoirment. The impact of

renal impairment on amprenavir elimination has not been studied. The renal elimination of unchanged amprenavir represents <3% of the administered dose.

Pediatric Patients: AGENERASE Oral Solution is contraindicated in infants and children below 4 years of age (see CONTRAINDICATIONS and WARNINGS).

The pharmacokinetics of amprenavir have been studied after either single or repeat doses of AGENERASE Capsules or Oral Solution in 84 pediatric patients. Twenty HIV-1-infected children ranging in age from 4 to 12 years received single doses from 5 mg/kg to 20 mg/kg using 25-mg or 150-mg capsules. The C_{max} of amprenavir increased less than proportionally with dose. The AUC_{0-∞} increased proportionally at doses between 5 and 20 mg/kg. Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules; therefore AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis.

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Table 2: Average (%CV) Pharmacokinetic Parameters in Children Ages 4 to 12 Years Receiving 20 mg/kg b.i.d. or 15 mg/kg t.i.d. of AGENERASE Oral Solution

		Cmax	t _{max}	AUC _{ss} *	Cave	Cmin	CL/F
Dose	n	(mcg/mL)	(hours)	(mcg•h/mL)	(mcg/mL)	(mcg/mL)	(mL/min/kg)
20 mg/kg		6.77	1.1	15.46	1.29	0.24	29
b.i.d.	20	(51%)	(21%)	(59%)	(59%)	(98%)	(58%)
15 mg/kg		3.99	1.4	8.73	1.09	0.27	32
t.i.d.	17	(37%)	(90%)	(36%)	(36%)	(95%)	(34%)

*AUC is 0 to 12 hours for b.i.d. and 0 to 8 hours for t.i.d., therefore the Cave is a better comparison of the exposures.

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Geriatric Patients: The pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

Gender: The pharmacokinetics of amprenavir do not differ between males and females. Females may have a lower amount of alcohol dehydrogenase compared with males and may be at increased risk of propylene glycol-associated adverse events; no data are available on propylene glycol metabolism in females.

167	Race: The pharmacokinetics of amprenavir do not differ between Blacks and
168	non-Blacks. Certain ethnic populations (Asians, Eskimos, and Native Americans) may be
169	at increased risk of propylene glycol-associated adverse events because of alcohol
170	dehydrogenase polymorphisms; no data are available on propylene glycol metabolism in
171	these groups.
172	Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and
173	PRECAUTIONS: Drug Interactions.
174	Amprenavir is metabolized in the liver by the cytochrome P450 enzyme system.
175	Amprenavir inhibits CYP3A4. Caution should be used when coadministering medications
176	that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that
177	are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9,
178	CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).
179	Drug interaction studies were performed with amprenavir capsules and other drugs
180	likely to be coadministered or drugs commonly used as probes for pharmacokinetic
181	interactions. The effects of coadministration of amprenavir on the AUC, C _{max} , and C _{min} are
182	summarized in Table 3 (effect of other drugs on amprenavir) and Table 4 (effect of
183	amprenavir on other drugs). For information regarding clinical recommendations, see
184	PRECAUTIONS.
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Table 3: Drug Interactions: Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadministered Drug

				% Change in	Amprenavir Ph	armacokinetic
Co-	Dose of				Parameters*	
administered	Coadministered	Dose of			(90% CI)	
Drug	Drug	AGENERASE	n	Cmex	AUC	C _{man}
	300 mg b.i.d.	900 mg b.i.d.		↑ 47	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	↑27
Abacavir	for 3 weeks	for 3 weeks	4	(15 to 154)	(↓ 18 to ↑ 103)	(√ 46 to ↑ 197)
	500 mg b.i.d.	1200 mg b.i.d.		个15	↑18	个39
Clarithromycin	for 4 days	for 4 days	12	(个1 to 个31)	(个8 to 个29)	(个31 to 个47)
	800 mg t.i.d.	750 or 800 mg				
	for 2 weeks	t.i.d. for 2 weeks		↑ 18	↑ 33	↑ 25
Indinavir	(fasted)	(fasted)	9	(13 to ↑58)	(个2 to 个73)	(√27 to ↑116)
	400 mg	1200 mg		↓ 16	个31	•
Ketoconazole	single dose	single dose	12	(√ 25 to √ 6)	(个20 to 介42)	NA
	150 mg	600 mg		⇔	⇔	
Lamivudine	single dose	single dose	11	(↓ 17 to ↑ 9)	(↓ 15 to ↑ 14)	NA
	750 mg t.i.d.	750 or 800 mg				
	for 2 weeks	t.i.d. for 2 weeks		↓ 14	⇔	189
Nelfinavir	(fed)	(fed)	6	(√ 38 to ↑ 20)	(↓ 19 to ↑ 47)	(↑ 52 to ↑ 448
-	300 mg q.d.	1200 mg b.i.d.		⇔	↓ 15	↓ 15
Rifabutin	for 10 days	for 10 days	5	(1 ± 21 to ↑10)	(√ 28 to 0)	(√ 38 to ↑ 17)
	300 mg	1200 mg b.i.d.		↓ 70	¥ 82	↓ 92
Rifampin	q.d. for 4 days	for 4 days	11	(√ 76 to √ 62)	(√84 to √ 78)	(1 95 to 1 89)
	800 mg t.i.d.	750 or 800 mg				
	for 2 weeks	t.i.d. for 2 weeks		↓ 37	↓ 32	↓ 14
Saquinavir	(fed)	(fed)	7	(√54 to √14)	(√ 49 to √ 9)	(√ 52 to ↑ 54)
	300 mg	600 mg		⇔	个13	
Zidovudine	single dose	single dose	12	(√ 5 to ↑ 24)	(少 2 to 个 31)	NA.

^{*}Based on total-drug concentrations.

 $\uparrow = \text{Increase}; \downarrow = \text{Decrease}; \Leftrightarrow = \text{No change (}\uparrow \text{ or } \downarrow < 10\%); \text{NA} = C_{\min} \text{ not calculated for}$ 190 single-dose study.

				% Change in	Pharmacokinetic	Parameters of
Со-	Dose of Co-			Coadministered Drug		
administered	administered	Dose of			(90% CI)	
Drug	Drug	AGENERASE	n	- C _{max}	AUC	Cmm
	500 mg b.i.d.	1200 mg b.i.d.		V 10	\$	0
Clarithromycin	for 4 days	for 4 days	12	(√ 24 to ↑ 7)	(↓17 to ↑11)	(↓ 13 to ↑ 20)
	400 mg	1200 mg		个19	↑ 44	
Ketoconazole	single dose	single dose	12	(个8 to 个33)	(个31 to 个59)	NA
	150 mg	600 mg		⇔	⇔	
Lamivudine	single dose	single dose	11	(√ 17 to ↑ 3)	(√ 11 to 0)	NA
	300 mg q.d.	1200 mg b.i.d.		. 个119	↑193	个271
Rifabutin	for 10 days	for 10 days	5	(个82 to 个164)	(个156 to 个235)	(个17Ï to 个409)
	300 mg	1200 mg b.i.d.		⇔	. ⇔	
Rifampin	q.d. for 4 days	for 4 days	11	(√ 13 to ↑ 12)	(↓ 10 to ↑ 13)	ND
	300 mg	600 mg		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	↑31	
Zidovudine	single dose	single dose	12	(个14 to 个71)	(个19 to 个45)	NA

↑ = Increase; \downarrow = Decrease; \Leftrightarrow = No change (↑ or \downarrow <10%); NA = C_{min} not calculated for single-dose study; ND = Interaction cannot be determined as C_{min} was below the lower limit of quantitation.

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Nucleoside Reverse Transcriptase Inhibitors (NRTIs): There was no effect of amprenavir on abacavir in subjects receiving both agents based on historical data.

amprenavir on abacavir in subjects receiving both agents based on historical data.

HIV Protease Inhibitors: The effect of amprenavir on total drug concentrations of other
HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons
to historical data. Indinavir steady-state C_{max}, AUC, and C_{min} were decreased by 22%,
38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and
AUC were seen after the first dose. Saquinavir steady-state C_{max}, AUC, and C_{min} were
increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant

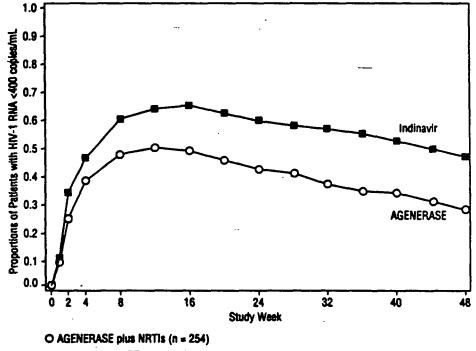
amprenavir. Nelfinavir steady-state C_{max} , AUC, and C_{min} were increased by 12%, 15%, and

207 14%, respectively, by concomitant amprenavir.

208	For information regarding clinical recommendations, see PRECAUTIONS: Drug
209	Interactions.
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211	INDICATIONS AND USAGE: AGENERASE (amprenavir) is indicated in
212	combination with other antiretroviral agents for the treatment of HIV-1 infection.
213	The following points should be considered when initiating therapy with
214	AGENERASE:
215	In a study of NRTI-experienced, protease inhibitor-naive patients,
216	AGENERASE was found to be significantly less effective than indinavir (see
217	Description of Clinical Studies).
218	Mild to moderate gastrointestinal adverse events led to discontinuation of
219	AGENERASE primarily during the first 12 weeks of therapy (see ADVERSE
220	REACTIONS).
221	There are no data on response to therapy with AGENERASE in protease
222	inhibitor-experienced patients.
223	AGENERASE Oral Solution should be used only when AGENERASE Capsules or
224	other protease inhibitor formulations are not therapeutic options.
225	Description of Clinical Studies: Therapy-Naive Adults: PROAB3001, a randomized,
226	double-blind, placebo-controlled, multicenter study, compared treatment with
227	AGENERASE Capsules (1200 mg twice daily) plus lamivudine (150 mg twice daily) plus
228	zidovudine (300 mg twice daily) versus lamivudine (150 mg twice daily) plus zidovudine
229	(300 mg twice daily) in 232 patients. Through 24 weeks of therapy, 53% of patients
230	assigned to AGENERASE/zidovudine/lamivudine achieved HIV RNA <400 copies/mL.
231	Through week 48, the antiviral response was 41%. Through 24 weeks of therapy, 11% of
232	patients assigned to zidovudine/lamivudine achieved HIV RNA <400 copies/mL_Antivira
233	response beyond week 24 is not interpretable because the majority of patients discontinued
234	or changed their antiretroviral therapy.
235	NRTI-Experienced Adults: PROAB3006, a randomized, open-label multicenter study,
236	compared treatment with AGENERASE Capsules (1200 mg twice daily) plus NRTIs
237	versus indinavir (800 mg every 8 hours) plus NRTIs in 504 NRTI-experienced, protease
238	inhibitor-naive patients, median age 37 years (range 20 to 71 years), 72% Caucasian, 80%

male, with a median CD4 cell count of 404 cells/mm³ (range 9 to 1706 cells/mm³) and a median plasma HIV-1 RNA level of 3.93 log₁₀ copies/mL (range 2.60 to 7.01 log₁₀ copies/mL) at baseline. Through 48 weeks of therapy, the median CD4 cell count increase from baseline in the amprenavir group was significantly lower than in the indinavir group, 97 cells/mm³ versus 144 cells/mm³, respectively. There was also a significant difference in the proportions of patients with plasma HIV-1 RNA levels <400 copies/mL through 48 weeks (see Figure 1 and Table 5).

Figure 1: Virologic Response Through Week 48, PROAB3006*,1



■ Indinavir plus NRTIs (n = 250)

*Roche AMPLICOR HIV-1 MONITOR assay.

*Discontinuations and missing data were considered as HIV-1 RNA ≥400 copies/mL.

HIV-1 RNA status and reasons for discontinuation of randomized treatment at 48 weeks are summarized (Table 5).

253 Table 5: Outcomes of Randomized Treatment Through Week 48 (PROAB3006)

	AGENERASE	Indinavir
Outcome	(n = 254)	(n = 250)
HIV RNA <400 copies/mL*	30%	49%
HIV RNA ≥400 copies/mL ^{1,‡}	38%	26%
Discontinued due to adverse events**	16%	12%
Discontinued due to other reasons ^{‡,§}	16%	13%

- *Corresponds to rates at Week 48 in Figure 1.
- [†]Virological failures at or before Week 48.
- [‡]Considered to be treatment failure in the analysis.
- 257 Includes discontinuations due to consent withdrawn, loss to follow-up, protocol
- violations, non-compliance, pregnancy, never treated, and other reasons.

260 CONTRAINDICATIONS: Because of the potential risk of toxicity from the large

- amount of the excipient propylene glycol, AGENERASE Oral Solution is
- 262 contraindicated in infants and children below the age of 4 years, pregnant women,
- 263 patients with hepatic or renal failure, and patients treated with disulfiram or
- 264 metronidazole (see WARNINGS and PRECAUTIONS).
- 265 Coadministration of AGENERASE is contraindicated with drugs that are highly
- dependent on CYP3A4 for clearance and for which elevated plasma concentrations
- are associated with serious and/or life-threatening events. These drugs are listed in
- 268 **Table 6.**

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Table 6: Drugs That are Contraindicated with AGENERASE

Drug Class	Drugs Within Class That Are CONTRAINDICATED with AGENERASE
Alcohol-dependence treatment	Disulfiram
Antibiotic	Metronidazole
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hyponotics	Midazolam, triazolam

AGENERASE is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product.

WARNINGS: ALERT: Find out about medicines that should not be taken with AGENERASE.

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and PRECAUTIONS).

Because of the possible toxicity associated with the large amount of propylene glycol and the lack of information on chronic exposure to large amounts of propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options. Certain ethnic populations (Asians, Eskimos, Native Americans) and women may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol; no data are available on propylene glycol

metabolism in these groups (see CLINICAL PHARMACOLOGY: Special

289 Populations: Gender and Race).

290	If patients require treatment with AGENERASE Oral Solution, they should be
291	monitored closely for propylene glycol-associated adverse events, including seizures,
292	stupor, tachycardia, hyperosmolality, lactic acidosis, renal toxicity, and hemolysis.
293	Patients should be switched from AGENERASE Oral Solution to AGENERASE
294	Capsules as soon as they are able to take the capsule formulation.
295	Use of alcoholic beverages is not recommended in patients treated with
296	AGENERASE Oral Solution.
297	Serious and/or life-threatening drug interactions could occur between amprenavir
298	and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine.
299	Concentration monitoring of these agents is recommended if these agents are used
300	concomitantly with AGENERASE (see CONTRAINDICATIONS).
301	Rifampin should not be used in combination with amprenavir because it reduces plasma
302	concentrations and AUC of amprenavir by about 90%.
303	Concomitant use of AGENERASE and St. John's wort (hypericum perforatum) or
304	products containing St. John's wort is not recommended. Coadministration of protease
305	inhibitors, including AGENERASE, with St. John's wort is expected to substantially
306	decrease protease inhibitor concentrations and may result in suboptimal levels of
307	amprenavir and lead to loss of virologic response and possible resistance to AGENERASE
308	or to the class of protease inhibitors.
309	Concomitant use of AGENERASE with lovastatin or simvastatin is not recommended.
310	Caution should be exercised if HIV protease inhibitors, including AGENERASE, are used
311	concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the
312	CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including
313	rhabdomyolysis, may be increased when HIV protease inhibitors, including amprenavir,
314	are used in combination with these drugs.
315	Particular caution should be used when prescribing sildenafil in patients receiving
316	amprenavir. Coadministration of AGENERASE with sildenafil is expected to substantially
317	increase sildenafil concentrations and may result in an increase in sildenafil-associated
318	adverse events, including hypotension, visual changes, and priapism (see
319	PRECAUTIONS: Drug Interactions and Information for Patients, and the complete
220	prescribing information for sildenafil)

321	Severe and life-threatening skin reactions, including Stevens-Johnson syndrome,
322	have occurred in patients treated with AGENERASE (see ADVERSE REACTIONS).
323	Acute hemolytic anemia has been reported in a patient treated with AGENERASE.
324	New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and
325	hyperglycemia have been reported during post-marketing surveillance in HIV-infected
326	patients receiving protease inhibitor therapy. Some patients required either initiation or
327	dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In
328	some cases, diabetic ketoacidosis has occurred. In those patients who discontinued
329	protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events
330	have been reported voluntarily during clinical practice, estimates of frequency cannot be
331	made and causal relationships between protease inhibitor therapy and these events have no
332	been established.
333	
334	PRECAUTIONS:
335	General: AGENERASE Capsules and AGENERASE Oral Solution are not
336	interchangeable on a milligram-per-milligram basis (see CLINICAL
337	PHARMACOLOGY: Pediatric Patients and CONTRAINDICATIONS).
338	Amprenavir is a sulfonamide. The potential for cross-sensitivity between drugs in the
339	sulfonamide class and amprenavir is unknown. AGENERASE should be used with caution
340	in patients with a known sulfonamide allergy.
341	AGENERASE is principally metabolized by the liver; therefore caution should be
342	exercised when administering this drug to patients with hepatic impairment (see DOSAGE
343	AND ADMINISTRATION).
344	Formulations of AGENERASE provide high daily doses of vitamin E (see Information
345	for Patients, DESCRIPTION, and DOSAGE AND ADMINISTRATION). The effects of
346	long-term, high-dose vitamin E administration in humans is not well characterized and has
347	not been specifically studied in HIV-infected individuals. High vitamin E doses may
348	exacerbate the blood coagulation defect of vitamin K deficiency caused by anticoagulant
349	therapy or malabsorption.
350	Patients with Hemophilia: There have been reports of spontaneous bleeding in patients
351	with hemophilia A and B treated with protease inhibitors. In some patients, additional

352	factor VIII was required. In many of the reported cases, treatment with protease inhibitors
353	was continued or restarted. A causal relationship between protease inhibitor therapy and
354	these episodes has not been established.
355	Fat Redistribution: Redistribution/accumulation of body fat, including central obesity,
356	dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and
357	"cushingoid appearance," have been observed in patients receiving protease inhibitors. The
358	mechanism and long-term consequences of these events are currently unknown. A causal
359	relationship has not been established.
360	Resistance/Cross-Resistance: Because the potential for HTV cross-resistance among
361	protease inhibitors has not been fully explored, it is unknown what effect amprenavir
362	therapy will have on the activity of subsequently administered protease inhibitors. It is also
363	unknown what effect previous treatment with other protease inhibitors will have on the
364	activity of amprenavir (see MICROBIOLOGY).
365	Information for Patients: A statement to patients and health care providers is included on
366	the product's bottle label: ALERT: Find out about medicines that should NOT be taken
367	with AGENERASE. A Patient Package Insert (PPI) for AGENERASE Oral Solution is
368	available for patient information.
369	AGENERASE Oral Solution is contraindicated in infants and children below the age of
370	4 years, pregnant women, patients with hepatic or renal failure, and patients treated with
371	disulfiram or metronidazole. AGENERASE Oral Solution should be used only when
372	AGENERASE Capsules or other protease inhibitor formulations are not therapeutic
373	options.
374	Patients treated with AGENERASE Capsules should be cautioned against switching to
375	AGENERASE Oral Solution because of the increased risk of adverse events from the large
376	amount of propylene glycol in AGENERASE Oral Solution.
377	Women, Asians, Eskimos, or Native Americans, as well as patients who have hepatic or
378	renal insufficiency, should be informed that they may be at increased risk of adverse events
379	from the large amount of propylene glycol in AGENERASE Oral Solution.
380	Patients should be informed that AGENERASE is not a cure for HIV infection and that
381	they may continue to develop opportunistic infections and other complications associated
382	with HIV disease. The long-term effects of AGENER ASE (amprenavir) are unknown at

383	this time. Patients should be told that there are currently no data demonstrating that therapy
384	with AGENERASE can reduce the risk of transmitting HIV to others through sexual
385	contact.
386	Patients should remain under the care of a physician while using AGENERASE.
387	Patients should be advised to take AGENERASE every day as prescribed. AGENERASE
388	must always be used in combination with other antiretroviral drugs. Patients should not
389	alter the dose or discontinue therapy without consulting their physician. If a dose is missed
390	patients should take the dose as soon as possible and then return to their normal schedule.
391	However, if a dose is skipped, the patient should not double the next dose.
392	Patients should inform their doctor if they have a sulfa allergy. The potential for
393	cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown.
394	AGENERASE may interact with many drugs; therefore, patients should be advised to
395	report to their doctor the use of any other prescription, nonprescription medication, or
396	herbal products, particularly St. John's wort.
397	Patients taking antacids (or the buffered formulation of didanosine) should take
398	AGENERASE at least 1 hour before or after antacid (or the buffered formulation of
399	didanosine) use.
400	Patients should be advised that drinking alcoholic beverages is not recommended while
401	taking AGENERASE Oral Solution.
402	Patients receiving sildenafil should be advised that they may be at an increased risk of
403	sildenafil-associated adverse events including hypotension, visual changes, and priapism,
404	and should promptly report any symptoms to their doctor.
405	Patients receiving hormonal contraceptives should be instructed that alternate
406	contraceptive measures should be used during therapy with AGENERASE.
407	High-fat meals may decrease the absorption of AGENERASE and should be avoided.
408	AGENERASE may be taken with meals of normal fat content.
409	Patients should be informed that redistribution or accumulation of body fat may occur in
410	patients receiving protease inhibitors and that the cause and long-term health effects of
A11	these conditions are not known at this time

412	Adult and pediatric patients should be advised not to take supplemental vitamin E since
413	the vitamin E content of AGENERASE exceeds the Reference Daily Intake (adults 30 IU,
414	pediatrics approximately 10 IU).
415	Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and
416	CLINICAL PHARMACOLOGY: Drug Interactions.
417	AGENERASE is an inhibitor of cytochrome P450 3A4 metabolism and
418	therefore should not be administered concurrently with medications with narrow
419	therapeutic windows that are substrates of CYP3A4. There are other agents that
420	may result in serious and/or life-threatening drug interactions (see
421	CONTRAINDICATIONS and WARNINGS).
422	Use of alcoholic beverages is not recommended in patients treated with AGENERASE
423	Oral Solution.
424	

425 Table 7: Drugs That Should Not Be Coadministered with AGENERASE

Table 7. Drugs Table 500	
Drug Class/Drug Name	Clinical Comment
	CONTRAINDICATED due to potential risk of toxicity from
Alcohol-dependence treatment:	the large amount of the exipient, propylene glycol, in
Disulfiram	AGENERASE Oral Solution.
	CONTRAINDICATED due to potential risk of toxicity from
Antibiotic:	the large amount of the exipient, propylene glycol, in
Metronidazole	AGENERASE Oral Solution.
Antihistamines:	CONTRAINDICATED due to potential for serious and/or
Astemizole, terfenadine	life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials:	May lead to loss of virologic response and possible resistance to
Rifampin	AGENERASE or to the class of protease inhibitors.
	CONTRAINDICATED due to potential for serious and/or
Ergot derivatives:	life-threatening reactions such as acute ergot toxicity
Dihydroergotamine, ergonovine,	characterized by peripheral vasospasm and ischemia of the
ergotamine, methylergonovine	extremities and other tissues.
GI motility agents:	CONTRAINDICATED due to potential for serious and/or
Cisapride	life-threatening reactions such as cardiac arrhythmias.
Herbal Products:	
St. John's wort (hypericum	May lead to loss of virologic response and possible resistance to
perforatum)	AGENERASE or to the class of protease inhibitors.
HMG Co-Reductase	
Inhibitors:	Potential for serious reactions such as risk of myopathy
Lovastatin, simvastatin	including rhabdomyolysis.
Neuroleptic:	CONTRAINDICATED due to potential for serious and/or life-
Pimozide	threatening reactions such as cardiac arrhythmias.
	CONTRAINDICATED due to potential for serious and/or life-
Sedative/hypnotics:	threatening reactions such as prolonged or increased sedation or
Midazolam, triazolam	respiratory depression.

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Table 8: Established and Other Potentially Significant Drug Interactions:

Alteration in Dose or Regimen May be Recommended Based on Drug Interaction

428 429

Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	. Clinical Comment			
	HIV-Antiviral Agents				
Non-nucleoside Reverse Transcriptase Inhibitors: Efavirenz, nevirapine	↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.			
Non-nucleoside Reverse	· =				

Transcriptase Inhibitor:		Appropriate doses of the combination with respect
Delavirdine	†Amprenavir	to safety and efficacy have not been established
Nucleoside Reverse	,	
Transcriptase Inhibitor:		
Didanosine (buffered		Take AGENERASE at least 1 hour before or after
formulation only)	↓Amprenavir	the buffered formulation of didanosine.
Tornulation only)		die buttered formulation of didanostrie.
	†Amprenavir	
	A	
HIV-Protease Inhibitors:	Amprenavir's effect on other	
Indinavir*.	I	
	protease inhibitors	Annanies dans costs and in the continue
lopinavir/ritonavir,	is not well	Appropriate doses of the combinations with respect
nelfinavir*, ritonavir	established.	to safety and efficacy have not been established.
	↓Amprenavir	·
	i	
	Amprenavir's	
	effect on	
HIV-Protease Inhibitor:	saquinavir is not	Appropriate doses of the combination with respect
Saquinavir*	well established.	to safety and efficacy have not been established.
	Othe	er Agents
	{ .	Take AGENERASE at least 1 hour before or after
Antacids	↓Amprenavir	antacids.
}]	Caution is warranted and therapeutic concentration
Antiarrhythmics:	į	monitoring is recommended for antiarrhythmics
Amiodarone, lidocaine		when coadministered with AGENERASE, if
(systemic), and quinidine	TAntiarrhythmics	available.
		Use with caution. Increased bepridil exposure may
Antiarrhythmic:		be associated with life-threatening reactions such
Bepridil	TBepridil	as cardiac arrhythmias.
		Concentrations of warfarin may be affected. It is
Anticoagulant:	İ	recommended that INR (international normalized
Warfarin		ratio) be monitored.
		Use with caution. AGENERASE may be less
Anticonvulsants:		effective due to decreased amprenavir plasma
Carbarnazepine,	, ,	concentrations in patients taking these agents
phenobarbital, phenytoin	↓ Amprenavir	concomitantly.
		Increase monitoring for adverse events due to
	1	ketoconazole or itraconazole. Dose reduction of
Antifungals:		ketoconazole or itraconazole may be needed for
Ketoconazole,	TKetoconazole	patients receiving more than 400 mg ketoconazole
itraconazole	Titraconazole	or itraconazole per day.
	· All de Criditation	A dosage reduction of rifabutin to at least half the
		recommended dose is required when
	1	AGENERASE and rifabutin are coadministered.*
	1	A complete blood count should be performed
	TRifabutin and	weekly and as clinically indicated in order to
Antimyschootspiele	rifabutin	monitor for neutropenia in patients receiving
Antimycobacterial: Rifabutin*	******	amprenavir and rifabutin.
	metabolite	ampicuavii and madduii.
Benzodiazepines:	<u> </u>	

Alprazolam, clorazepate,		Clinical significance is unknown; however, a
diazepam, flurazepam	†Benzodiazepines	decrease in benzodiazepine dose may be needed.
Calcium Channel		
Blockers:		
Diltiazem, felodipine,		
nifedipine, nicardipine,		
nimodipine, verapamil,		
amlodipine, nisoldipine,	TCalcium channel	Caution is warranted and clinical monitoring of
isradipine	blockers	patients is recommended.
		Use with caution. AGENERASE may be less
		effective due to decreased amprenavir plasma
Corticosteroid:		concentrations in patients taking these agents
Dexamethasone	↓Amprenavir	concomitantly.
Erectile Dysfunction		Use with caution at reduced doses of 25 mg every
Agent:	*	48 hours with increased monitoring for adverse
Sildenafil	TSildenafil	events.
1		Use lowest possible dose of atorvastatin or
FD4C Co.A. Podoston		cerivastatin with careful monitoring or consider
HMG-CoA Reductase	^	other HMG-CoA reductase inhibitors such as
Inhibitors: Atorvastatin, cerivastatin	TAtorvastatin,	pravastatin or fluvastatin in combination with AGENERASE.
	†Cerivastatin	
Immunosuppressants:	1	Therapeutic concentration monitoring is
Cyclosporine, tacrolimus,	†Immunosup-	recommended for immunosuppressant agents when coadministered with AGENERASE.
rapamycin	pressants	
	Effect on ethinyl	Alternative or additional contraceptive measures should be used when estrogen-based oral
Oral Contraceptive:	estradiol is not	contraceptives and AGENERASE are
Ethinyl estradiol	known.	coadministered.
Tricyclic	RIIOWII.	Therapeutic concentration monitoring is
Antidepressants:		recommended for tricyclic antidepressants when
Amitriptyline, imipramine	Tricyclics	coadministered with AGENERASE.
	1	

^{*}See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 3 and 4.

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Carcinogenesis and Mutagenesis: Long-term carcinogenicity studies of amprenavir in ---432 rodents are in progress. Amprenavir was not mutagenic or genotoxic in a battery of in vitro 433 and in vivo assays including bacterial reverse mutation (Ames), mouse lymphoma, rat 434 micronucleus, and chromosome aberrations in human lymphocytes. 435 Fertility: The effects of amprenavir on fertility and general reproductive performance 436 were investigated in male rats (treated for 28 days before mating at doses producing up to 437 twice the expected clinical exposure based on AUC comparisons) and female rats (treated 438 for 15 days before mating through day 17 of gestation at doses producing up to 2 times the 439 expected clinical exposure). Amprenavir did not impair mating or fertility of male or 440 female rats and did not affect the development and maturation of sperm from treated rats. 441

442	The reproductive performance of the F1 generation born to female rats given amprenavir
443	was not different from control animals.
444	Pregnancy and Reproduction: AGENERASE Oral Solution is contraindicated
445	during pregnancy due to the potential risk of toxicity to the fetus from the high
446	propylene glycol content. Therefore, if AGENERASE is used in pregnant women,
447	the AGENERASE Capsules formulation should be used (see complete prescribing
448	information for AGENERASE Capsules).
449	Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of
450	pregnant women exposed to AGENERASE, an Antiretroviral Pregnancy Registry
451	has been established. Physicians are encouraged to register patients by calling 1-
452	800-258-4263.
453	Nursing Mothers: The Centers for Disease Control and Prevention recommend that
454	HIV-infected mothers not breastfeed their infants to avoid risking postnatal
455	transmission of HIV. Although it is not known if amprenavir is excreted in human milk,
456	amprenavir is secreted into the milk of lactating rats. Because of both the potential for HIV
457	transmission and the potential for serious adverse reactions in nursing infants, mothers
458	should be instructed not to breastfeed if they are receiving AGENERASE.
459	Pediatric Use: AGENERASE Oral Solution is contraindicated in infants and children
460	below the age of 4 years due to the potential risk of toxicity from the excipient
461	propylene glycol (see CONTRAINDICATIONS and WARNINGS). Alcohol
462	dehydrogenase (ADH), which metabolizes propylene glycol, is present in the human fetal
463	liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are
464	limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or
465	greater than that observed in adults.
466	Two hundred fifty-one patients aged 4 and above have received amprenavir as single or
467	multiple doses in studies. An adverse event profile similar to that seen in adults was seen in
468	pediatric patients.
469	Geriatric Use: Clinical studies of AGENERASE did not include sufficient numbers of
470	patients aged 65 and over to determine whether they respond differently from younger
471	adults. In general, dose selection for an elderly patient should be cautious, reflecting the

472	greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant
473	disease or other drug therapy.
474	
475	ADVERSE REACTIONS: In clinical studies, adverse events leading to amprenavir
476	discontinuation occurred primarily during the first 12 weeks of therapy, and were mostly
477	due to gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain/discomfort),
478	which were mild to moderate in severity.
479	Skin rash occurred in 22% of patients treated with amprenavir in studies PROAB3001
480	and PROAB3006. Rashes were usually maculopapular and of mild or moderate intensity,
481	some with pruritus. Rashes had a median onset of 11 days after amprenavir initiation and a
482	median duration of 10 days. Skin rashes led to amprenavir discontinuation in
483	approximately 3% of patients. In some patients with mild or moderate rash, amprenavir
484	dosing was often continued without interruption; if interrupted, reintroduction of
485	amprenavir generally did not result in rash recurrence.
486	Severe or life-threatening rash (Grade 3 or 4), including cases of Stevens-Johnson
487	syndrome, occurred in approximately 1% of recipients of AGENERASE (see
488	WARNINGS). Amprenavir therapy should be discontinued for severe or
489	life-threatening rashes and for moderate rashes accompanied by systemic symptoms.
490	

Table 9: Selected Clinical Adverse Events of All Grades Reported in >5% of Adult

492 Patients

	PROAE	33001	PROAL	33006
	Therapy-Nai	ve Patients	NRTI-Experie	nced Patients
	AGENERASE*/	··		
	Lamivudine/	Lamivudine/	AGENERASE*/	
	Zidovudine	Zidovudine	NRTI	Indinavir/NRTI
Adverse Event	(n = 113)	(n = 109)	(n = 245)	(n = 241)
Digestive				
Nausea	74%	50%	43%	35%
Vomiting	34%	17%	24%	20%
Diarrhea or loose stools	39%	35%	60%	41%
Taste disorders	10%	6%	2%	8%
Skin				
Rash	27%	6%	20%	15%
Nervous				•
Paresthesia, oral/perioral	26%	6%	31%	2%
Paresthesia, peripheral	10%	4%	14%	10%
Psychiatric				
Depressive or mood disorders	16%	4%	9%	13%

*AGENERASE Capsules

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Among amprenavir-treated patients in Phase 3 studies, 2 patients developed de novo diabetes mellitus, 1 patient developed a dorsocervical fat enlargement (buffalo hump), and 9 patients developed fat redistribution.

498 499

Table 10: Selected Laboratory Abnormalities of All Grades Reported in ≥5% of Adult Patients

500

	PROAB	3001	PROAE	3006
	Therapy-Naiv	ve Patients	NRTI-Experier	nced Patients
·	AGENERASE*/			
	Lamivudine/	Lamivudine/	AGENERASE*/	
Laboratory Abnormality	Zidovudine	Zidovudine	NRTI	Indinavir/NRTI
(non-fasting specimens)	(n = 111)	(n = 108)	(n = 237)	(n =239)
Hyperglycemia (>116 mg/dL)	45%	31%	53%	58%
Hypertriglyceridemia				
(>213 mg/dL)	41%	27%	56%	52%
Hypercholesterolemia				
(>283 mg/dL)	7%	3%	13%	15%

*AGENERASE Capsules

502

503

505

501.

In studies PROAB3001 and PROAB3006, no increased frequency of Grade 3 or 4 AST,

ALT, amylase, or bilirubin elevations was seen compared to controls.

Pediatric Patients: An adverse event profile similar to that seen in adults was seen in

506 pediatric patients.

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OVERDOSAGE: There is no known antidote for AGENERASE. It is not known whether

amprenavir can be removed by peritoneal dialysis or hemodialysis. If overdosage occurs,

the patient should be monitored for evidence of toxicity and standard supportive treatment

applied as necessary.

AGENERASE Oral Solution contains large amounts of propylene glycol. In the event

of overdosage, monitoring and management of acid-base abnormalities is recommended.

Propylene glycol can be removed by hemodialysis.

515 516

518

DOSAGE AND ADMINISTRATION: AGENERASE may be taken with or without

food; however, a high-fat meal decreases the absorption of amprenavir and should be

avoided (see CLINICAL PHARMACOLOGY: Effects of Food on Oral Absorption).

Adult and pediatric patients should be advised not to take supplemental vitamin E
since the vitamin E content of AGENERASE Oral Solution exceeds the Reference
Daily Intake (adults 30 IU, pediatrics approximately 10 IU) (see DESCRIPTION).
The recommended dose of AGENERASE Oral Solution based on body weight and age
is shown in Table 10. Consideration should be given to switching patients from
AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to
take the capsule formulation (see WARNINGS).

Table 10: Recommended Dosages of AGENERASE Oral Solution

	Dose			
Age/Weight Criteria	b.i.d.	t.i.d.		
4 - 12 years	22.5 mg/kg	17 mg/kg		
or	(1.5 mL/kg)	(1.1 mL/kg)		
13 - 16 years and <50 kg	(maximum dose 2800 mg per day)	(maximum dose 2800 mg per day)		
13 - 16 years and ≥50 kg				
or				
>16 years	1400 mg	NA		

~ 533

Patients with Hepatic Impairment: AGENERASE Oral Solution is contraindicated in patients with hepatic failure (see CONTRAINDICATIONS).

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients with hepatic impairment. Based on a study with AGENERASE Capsules, adult patients with a Child-Pugh score ranging from 5 to 8 should receive a reduced dose of AGENERASE Oral Solution of 513 mg (34 mL) twice daily, and adult patients with a Child-Pugh score ranging from 9 to 12 should receive a reduced dose of AGENERASE Oral Solution of 342 mg (23 mL) twice daily (see CLINICAL PHARMACOLOGY: Hepatic Insufficiency).

AGENERASE Oral Solution has not been studied in children with hepatic impairment.

Renal Insufficiency: AGENERASE Oral Solution is contraindicated in patients with renal failure (see CONTRAINDICATIONS).

542	Patients with renal	impairment are at incre	eased risk of propylene glycol-associated
543	adverse events. AGENERASE Oral Solution should be used with caution in patients with		
544	renal impairment (see WARNINGS).		
545	AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable		
546	on a milligram-per-	milligram basis (see Cl	LINICAL PHARMACOLOGY).
547			
548	HOW SUPPLIED:		
549	AGENERASE Oral	Solution, a clear, pale ye	ellow to yellow, grape
550	bubblegum-pepperm	int-flavored liquid, cont	ains 15 mg of amprenavir in each 1 mL.
551	Bottles of 240 mL	with child-resistant clos	sures (NDC 0173-0687-00). This product does
552	not require reconstitu	ition.	
553	Store at controlle	d room temperature o	f 25°C (77°F) (see USP).
554			
555			Licensed from
556	GlaxoWello	ome	VERTEX.
557	Glaxo Wellcome Inc		Vertex Pharmaceuticals Incorporated
558	Research Triangle Pa	ark, NC 27709	Cambridge, MA 02139
559	5	,	
560	AGENERASE is a re	egistered trademark of the	he Glaxo Wellcome group of companies.
561		•	
562	US Patent Nos. 5,585	5,397; 5,723,490; and 5,	646,180
563			
564	©2001, Glaxo Wellc	ome Inc. All rights reser	rved.
565		•	
566	Date of Issue	RL no. –	
567			
568	PHARMACIST	-DETACH HERE ANI	O GIVE INSTRUCTIONS TO PATIENT
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572	PATIENT INFORMATION
573	
574	AGENERASE® (amprenavir) Oral Solution
575	
576	ALERT: Find out about medicines that should not be taken with AGENERASE.
577	Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH
578	AGENERASE."
579	
580	Please read this information before you start taking AGENERASE (pronounced ah-GEN-
581	er-ase) Oral Solution, and re-read it each time you receive your prescription, just in case
582	something has changed. Remember that this information does not take the place of careful
583	discussions with your doctor when you start this medication and at checkups. You should
584	not change or stop your anti-HIV treatment without first talking with your doctor. You
585	should tell your doctor about any drug you are taking or planning to take because
586	taking AGENERASE Oral Solution with some medications can result in serious or
587	life-threatening problems.
588	·
589	What is AGENERASE Oral Solution?
590	AGENERASE Oral Solution is a medication used to treat HIV infection. HIV is the virus
591	that causes AIDS (acquired immune deficiency syndrome). AGENERASE Oral Solution is
592	taken by mouth as an oral solution. It belongs to a class of anti-HIV medicines called
593	protease inhibitors.
594	
595	What is the Important Safety Information on AGENERASE Oral Solution?
596	AGENERASE Oral Solution should not be used in infants and children below the age of
597	4 years, pregnant women, patients with liver or kidney failure, and patients receiving
598	disulfiram (ANTABUSE®) or metronidazole (FLAGYL®).
599	
600	AGENERASE Oral Solution contains a large amount of propylene glycol, a liquid needed
601	to dissolve amprenavir. Because of the possible side effects of the large amount of
602	propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE

603	Capsules or other protease inhibitor formulations are not options. You should not switch
604	from AGENERASE Capsules to AGENERASE Oral Solution without talking to your
605	doctor.
606	• ···
607	If you are a woman or an Asian, Eskimo, or Native American, or if you have liver or
608	kidney disease, you may be at increased risk of side effects from the large amount of
609	propylene glycol in AGENERASE Oral Solution.
610	
611	How does AGENERASE Oral Solution work?
612	AGENERASE Oral Solution is used only in combination with other anti-HIV medicines.
613	When used in combination therapy, AGENERASE Oral Solution may help lower the
614	amount of HIV found in your blood, raise CD4 (T) cell count, and keep your immune
615	system as healthy as possible so that it can help fight infection. However, AGENERASE
616	Oral Solution does not have these effects in all patients.
617	
618	What are the side effects of AGENERASE Oral Solution?
619	Common side effects of AGENERASE Oral Solution are nausea, vomiting, diarrhea, rash,
620	and a tingling sensation around the mouth. Severe or life-threatening rash has been
621	reported.
622	
623	Possible side effects from the large amount of propylene glycol in AGENERASE Oral
624	Solution include seizures, drowsiness, fast heart rate, and kidney and blood abnormalities.
625	
626	Contact your doctor if you have nausea, vomiting, diarrhea, or rash. Your doctor may be
627	able to help you manage these symptoms. Your doctor will advise you whether your
628	symptoms can be managed on therapy or whether AGENERASE Oral Solution should be
629	stopped.
630	
631	This list of side effects is not complete. Your doctor or pharmacist can discuss with you a
632	more complete list of possible side effects with AGENERASE Oral Solution. Talk to your
' 632	destar promotive shout any side offeets you have

634		
635	How should I take AGENERASE Oral Solution?	
636	Take AGENERASE Oral Solution exactly as your doctor prescribes it. AGENERASE Oral	
637	Solution can be taken with or without food. However, you should not take AGENERASE	
638	with a high-fat meal because this could reduce the effectiveness of AGENERASE Oral	
639	Solution.	
640		
641	What should I do if I miss a dose of AGENERASE Oral Solution?	
642	To help make sure that your anti-HIV therapy is as effective as possible, be very careful to	
643	take all of your medication exactly as your doctor prescribed it and do not skip any doses.	
644		
645	If you miss a dose of AGENERASE Oral Solution by more than 4 hours, wait and take the	
646	next dose at the regularly scheduled time. However, if you miss a dose by fewer than	
647	4 hours, take your missed dose immediately. Then take your next dose at the regularly	
648	scheduled time. Do not take more or less than your prescribed dose of AGENERASE Oral	
649	Solution at any one time.	
650		
651	When your supply of AGENERASE Oral Solution or other anti-HIV drugs starts to run	
652	low, arrange to get more from your doctor or pharmacy. It is very important that you take	
653	anti-HIV drugs as prescribed by your doctor because the amount of virus in your blood	
654	may increase if one or more of the drugs is stopped, even for a short time.	
655		
656	Can AGENERASE Oral Solution be taken with other medications?	
657	Protease inhibitors, including AGENERASE, may interact with other drugs, including	
658	those you take without a prescription. Before you take AGENERASE, tell your doctor	
659	about any drugs that you are taking or planning to take, including nonprescription drugs:	
660	MEDICINES YOU SHOULD NOT TAKE WITH AGENERASE	
661	AGENERASE Oral Solution should <u>not</u> be taken with ANTABUSE (disulfiram) or	
662	FLAGYL (metronidazole).	
663		

664	Drinking alcoholic beverages is not recommended while taking AGENERASE Oral		
665	Solution because it may increase side effects related to propylene glycol content.		
666			
667	•	You should not take any of the following me	dications with AGENERASE Oral
668		Solution because serious or life-threatening	problems could occur.*
669		HALCION® (triazolam)	PROPULSID® (cisapride)
670		HISMANAL [®] (asternizole)	VERSED [®] (midazolam)
671		Ergot medications (CAFERGOT® and others)	VASCOR® (bepridil)
672		ORAP® (pimozide)	SELDANE® (terfenadine)
673			
674	•	You should also not take rifampin with AGE	NERASE Oral Solution because this
675	drug reduces the effectiveness of AGENERASE. Rifampin is also known as:		
676	RIFADIN®, RIFAMATE®, RIFATER®, and RIMACTANE®.		IMACTANE [®] .
677			
678	•	Taking AGENERASE with St. John's Wort (hy	ypericum perforatum, a nonprescription
679	herbal product) or products containing St. John's Wort is not recommended. Talk with		
680	your doctor if you are taking or are planning to take St. John's Wort because St. John		
681		Wort may reduce the effect of AGENERASE.	
682			
683	•	It is not recommended that you take AGENER.	ASE with the cholesterol-lowering drug
684	MEVACOR® (lovastatin) or ZOCOR® (simvastatin) because of the possible drug		
685	interactions. There is also an increased risk of drug interactions between		
686	AGENERASE and LIPITOR® (atorvastatin), and BAYCOL® (cerivastatin). Talk to		nd BAYCOL® (cerivastatin). Talk to
687	your doctor if you are taking or are planning to take these or other drugs for lowering		
688		cholesterol.	
689		• · · · · · · · · · · · · · · · · · · ·	
690	N	fedicines That Require Dose Adjustments or S	pecial Attention From Your Doctor
691	•	Serious and/or life-threatening drug interact	tions can also occur if you take
692		AGENERASE Oral Solution with any of the	following drugs.* If you need to take
693		any of these drugs, your doctor may closely mo	onitor the amount of drug in your blood
694		to minimize potential problems.	

695		CORDARONE® (amiodarone)
696		Phenobarbital
697		TEGRETOL®, CARBATROL® (carbamazepine)
698		DILANTIN® (phenytoin)
699		Lidocaine
700		COUMADIN® (warfarin)
701		(quinidine) QUINAGLUTE®, CARDIOQUIN®, QUINIDEX®
702		Antidepressants such as ELAVIL® (amitriptyline), NORPRAMIN® (desipramine),
703		PAMELOR® (nortriptyline), TOFRANIL® (imipramine)
704		
705	•	Tell your doctor about any drugs that you are taking or planning to take, including
706	-	nonprescription drugs.
707		
708	•	Before you take VIAGRA® (sildenafil) with AGENERASE Oral Solution, talk to your
709		doctor about possible drug interactions and side effects. If you take VIAGRA and
710		AGENERASE Oral Solution together, you may be at increased risk of side effects of
711		VIAGRA such as low blood pressure, visual changes, and penile erection lasting more
712		than 4 hours. If an erection lasts longer than 4 hours, you should seek immediate
713		medical assistance to avoid permanent damage to your penis. Your doctor can explain
714		these symptoms to you.
715		
716	•	If you use birth control pills, talk to your doctor about choosing a different type of
717		contraceptive, since AGENERASE Oral Solution may reduce the effectiveness of some
718		birth control pills.
719		•
720	•	Because AGENERASE Oral Solution contains large amounts of vitamin E, you should
721		not take additional vitamin E while taking AGENERASE Oral Solution.
722		<u>.</u>
723	•	•
774	•	Special considerations:*

725	If you take AGENERASE Oral Solution with MYCOBUTIN' (fitabutin), your doctor	
726	will lower the dose of MYCOBUTIN.	
727	If you take AGENERASE Oral Solution with VIDEX® (didanosine, ddI)(buffered	
728	formulation), take them at least 1 hour apart.	
729	If you take AGENERASE Oral Solution with antacids, take them at least 1 hour apart	
730		
731	Does AGENERASE Oral Solution cure HIV infection or AIDS?	
732	AGENERASE Oral Solution does not cure HIV infection or AIDS. At this time we do no	
733	know if AGENERASE will help you live longer or have fewer of the medical problems	
734	(opportunistic infections) that are associated with HIV infection or AIDS. Because of this	
735	you must be sure to be seen regularly by your healthcare professional.	
736		
737	Does AGENERASE Oral Solution reduce the risk of passing HIV to others?	
738	No. AGENERASE Oral Solution, as well as other anti-HIV medications, has not been	
739	shown to reduce the risk of passing HIV to others through sexual contact or blood	
740	contamination. Continue to practice safe sex and do not use or share dirty needles.	
741		
742	Who should not take AGENERASE Oral Solution?	
743	AGENERASE Oral Solution should not be used in infants and children below 4 years of	
744	age, pregnant women, patients with liver or kidney failure, or patients on disulfiram	
745	(ANTABUSE) or metronidazole (FLAGYL).	
746		
747	Do not take AGENERASE Oral Solution if you have had a serious allergic reaction to	
748	AGENERASE Oral Solution or any of its ingredients. If you have liver disease, your	
749	dosage of AGENERASE Oral Solution may have to be adjusted.	
750		
751	If you are allergic to sulfa drugs, you should inform your doctor.	
752		
753	Can children take AGENERASE Oral Solution?	
754	AGENERASE Oral Solution should not be used in infants and children below 4 years of	
755	age.	

756		
757	Children from 4 to 12 years of age can take AGENERASE Oral Solution. Your doctor will	
758	tell you if the oral solution or capsule is best for your child. Your child's doctor will decide	
759	the right dose based on your child's weight and age.	
760		
761	Can pregnant women and nursing mothers take AGENERASE Oral Solution?	
762	AGENERASE Oral Solution should not be used by pregnant women. Talk to your doctor	
763	if you are pregnant or if you become pregnant while taking AGENERASE Oral Solution.	
764		
765	Mothers with HIV should not breastfeed their infants because HIV in the breast milk can	
766	infect the infant.	
767		
768	What other medical conditions should I discuss with my doctor?	
769	Talk to your doctor if you are pregnant or if you become pregnant while you are taking	
770	AGENERASE Oral Solution.	
771		
772	Also talk to your doctor if you have hemophilia or problems with your liver or kidneys.	
773		
774	How should I store AGENERASE Oral Solution?	
775	AGENERASE Oral Solution should be stored at room temperature and should not be	
776	refrigerated.	
777		
778	Other information:	
779	This medication is prescribed for a particular condition. Do not use it for any other	
780	condition or give it to anybody else. Keep AGENERASE Oral Solution and all medicines	
781	out of the reach of children.	
782	.	
783	Ask a healthcare professional any questions you may have about AGENERASE Oral	
784	Solution.	
785		
786	AGENERASE is a registered trademark of the Glaxo Wellcome group of companies.	

787			
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789	Glaxo Wellcome group of companies. The makers of these brands are not affiliated with		
790	and do not endorse Glaxo Wellcome or its products.		
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